



## Review

# From Bush Medicine to Modern Phytopharmaceutical: A Bibliographic Review of Devil's Claw (*Harpagophytum* spp.)

Thomas Brendler <sup>1,2</sup>

<sup>1</sup> Department of Botany and Plant Biotechnology, University of Johannesburg, Auckland Park, Johannesburg 2006, South Africa; txb@plantaphile.eu

<sup>2</sup> Plantaphile, Collingswood, NJ 08108, USA

**Abstract:** Devil's claw (*Harpagophytum* spp., Pedaliaceae) is one of the best-documented phyto-medicines. Its mode of action is largely elucidated, and its efficacy and excellent safety profile have been demonstrated in a long list of clinical investigations. The author conducted a bibliographic review which not only included peer-reviewed papers published in scientific journals but also a vast amount of grey literature, such as theses and reports initiated by governmental as well as non-governmental organizations, thus allowing for a more holistic presentation of the available evidence. Close to 700 sources published over the course of two centuries were identified, confirmed, and cataloged. The purpose of the review is three-fold: to trace the historical milestones in devil's claw becoming a modern herbal medicine, to point out gaps in the seemingly all-encompassing body of research, and to provide the reader with a reliable and comprehensive bibliography. The review covers aspects of ethnobotany, taxonomy, history of product development and commercialization, chemistry, pharmacology, toxicology, as well as clinical efficacy and safety. It is concluded that three areas stand out in need of further investigation. The taxonomical assessment of the genus is outdated and lacking. A revision is needed to account for intra- and inter-specific, geographical, and chemo-taxonomical variation, including variation in composition. Further research is needed to conclusively elucidate the active compound(s). Confounded by early substitution, intermixture, and blending, it has yet to be demonstrated beyond a reasonable doubt that both (or all) *Harpagophytum* spp. are equally (and interchangeably) safe and efficacious in clinical practice.

**Keywords:** *Harpagophytum*; devil's claw; teufelskralle; grapple plant; sengaparile; harpagoside; nomenclature; ethnobotany; traditional use; trade; biochemistry; pharmacology; clinical; safety; toxicology; veterinary; review



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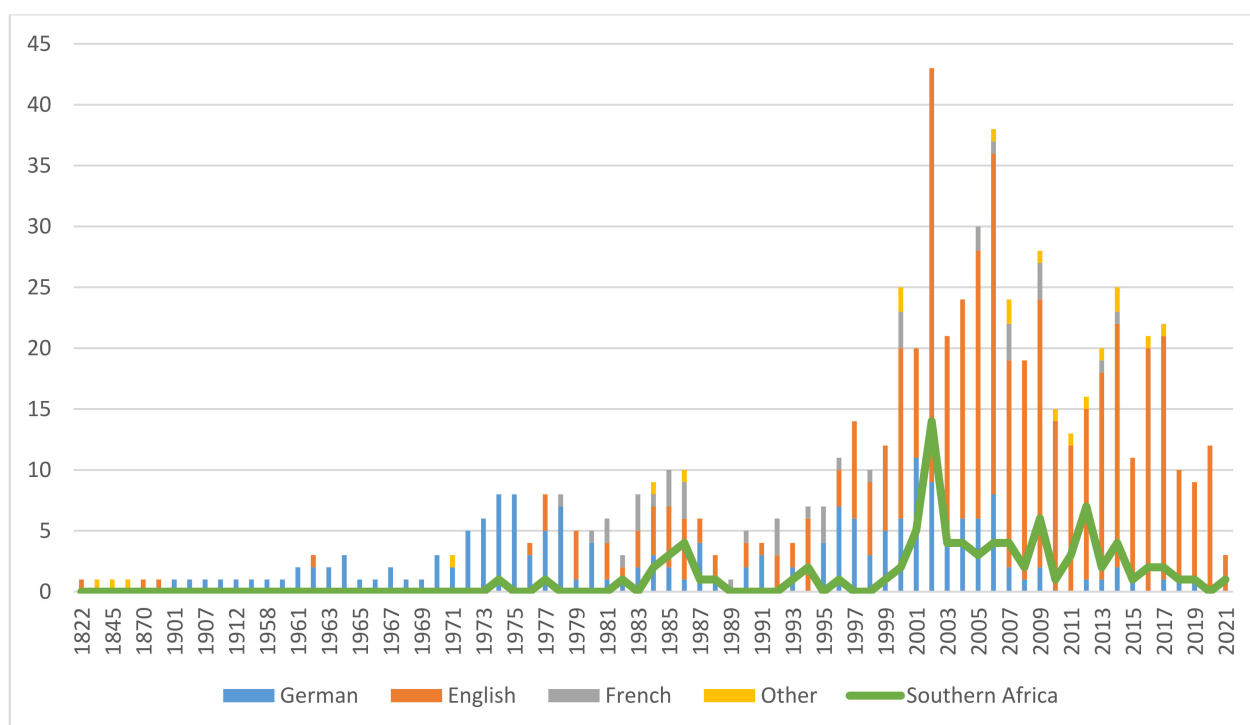
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## 1. Introduction

Devil's claw is the collective name of plants from the genus *Harpagophytum* (Pedaliaceae). The latter includes two species, *H. procumbens* (Burch.) DC. ex Meisn. and *H. zeyheri* Decne., currently divided into five subspecies with introgression reported from overlapping habitats [1,2]. The secondary root tubers of devil's claw are used in botanical drugs and supplements and are exported from Southern Africa, mainly Namibia. Entrepreneurial spirit, colonialism, and the absence of regulatory barriers drove the commercialization of devil's claw in a fashion similar to that of other medicinal plants from Southern Africa, such as Umckaloabo (*Pelargonium sidoides*) [3], rooibos (*Aspalathus linearis*) and honeybush (*Cyclopia* spp.) [4], buchu (*Agathosma betulina*) [5], cape aloe (*Aloe ferox*) [6], uzara (*Xysmalobium undulatum*) [7], and to some extent, hoodia (*Hoodia gordonii*) [8], among others [9]. From the 1960s onward, products quickly gained popularity, initially in Germany, then France, and by the mid-1980s, all over the developed world. This led to an increase in demand and consequently harvesting pressure in the countries of origin, to the point that devil's claw was briefly considered to be listed on CITES appendix II [10]. However, ongoing efforts to introduce good harvesting practices and cultivation attempts helped supply to become more sustainable.

Once harvested, botanical differentiation between species and subspecies is virtually impossible, and it can safely be assumed that since the 1970s, the product of commerce is one or the other and often of mixed origin [11–14]. Thus, current official compendia do not distinguish between the two botanical sources of devil’s claw but require compliance in terms of contents of the marker compound harpagoside, a cinnamoylated iridoid glucoside. The primary medicinal uses of devil’s claw are the management of arthritis, pain, and dyspepsia [15,16]. An impressive number of clinical trials, the earlier being mostly observational, the more recent randomized, placebo-controlled studies—albeit being of variable quality—indicate clinical efficacy and safety [17]. However, whether harpagoside is more than a just marker, but also the (only) active compound, remains to be demonstrated. Consequently, superiority of *H. procumbens* over *H. zeyheri* cannot be derived merely from harpagoside content [18]. Lower levels of harpagoside do not necessarily translate to lower levels of total iridoids, and phytochemically distinct extracts from *H. procumbens* and *H. zeyheri* have shown similar in vivo analgesic and anti-inflammatory properties [19].

The vast body of evidence presented here—over a period of 55 years, about one general review per year was published in the scientific literature [20–80], not counting reviews specific to clinical efficacy (see Section 11.1.)—makes devil’s claw one of the best-researched botanicals. Figure 1 illustrates the growing and sustained research interest. The 694 included publications were grouped by language, which yielded a perspective on how research interest spread geographically over time. Despite English becoming the lingua franca of science toward the end of the 20th century, a trend is clearly noticeable—from Germany to France to the rest of the world—and confirmed by research, trade, and availability and popularity of pharmaceutical products. An interesting discrepancy reveals itself when comparing the total with the research output of the region of origin. Nonetheless, knowledge gaps concerning species interchangeability remain to be closed, the elucidation of which is one purpose of this review. It is hoped that the assembly of this extensive bibliography will stimulate further research of this interesting genus of medicinal plants.



**Figure 1.** Publications on *Harpagophytum* spp., 1822–2021 (colors indicate publication language/origin of research).

## 2. Materials and Methods

Multiple searches were conducted in the PubMed, Scopus, and Google Scholar databases with the following keywords and combinations thereof: “*Harpagophytum*, harpagophyton, devil’s claw, Teufelskralle, grapple plant, sengaparile, garra-do-diabo, griffe du diable, (h)arpagoside, taxonomy, nomenclature, ethnobotany, traditional use, ecology, cultivation, sustainability, economy, trade, CITES, chemistry, biochemistry, compounds, pre-clinical, pharmacology, clinical, RCT, safety, toxicology, veterinary, review”. Union catalogues were also searched. The search was limited to scientific literature, and popular magazines and compendia were excluded. Also excluded were articles which only mentioned *Harpagophytum* without elaboration. Further excluded were reports on compounds present in *Harpagophytum*, that were derived from other sources (e.g., harpagoside from *Scrophularia* spp.).

Reference sections of selected publications were searched manually. Academic theses were retrieved primarily via the Bielefeld Academic Search Engine (BASE). Patents were retrieved from the European, US, and international (WIPO) patent office databases.

A substantial body of publications (125) was identified addressing aspects of ecology, stakeholders’ livelihoods, efforts in capacity building, as well as access-benefit-sharing (ABS) and its legislation. They are included in the publication statistics (see Figure 1). In reviewing the pharmaceutical history of devil’s claw, however, these topics appear out of scope and will be reviewed in a separate publication. Figure 2 illustrates the selection process.

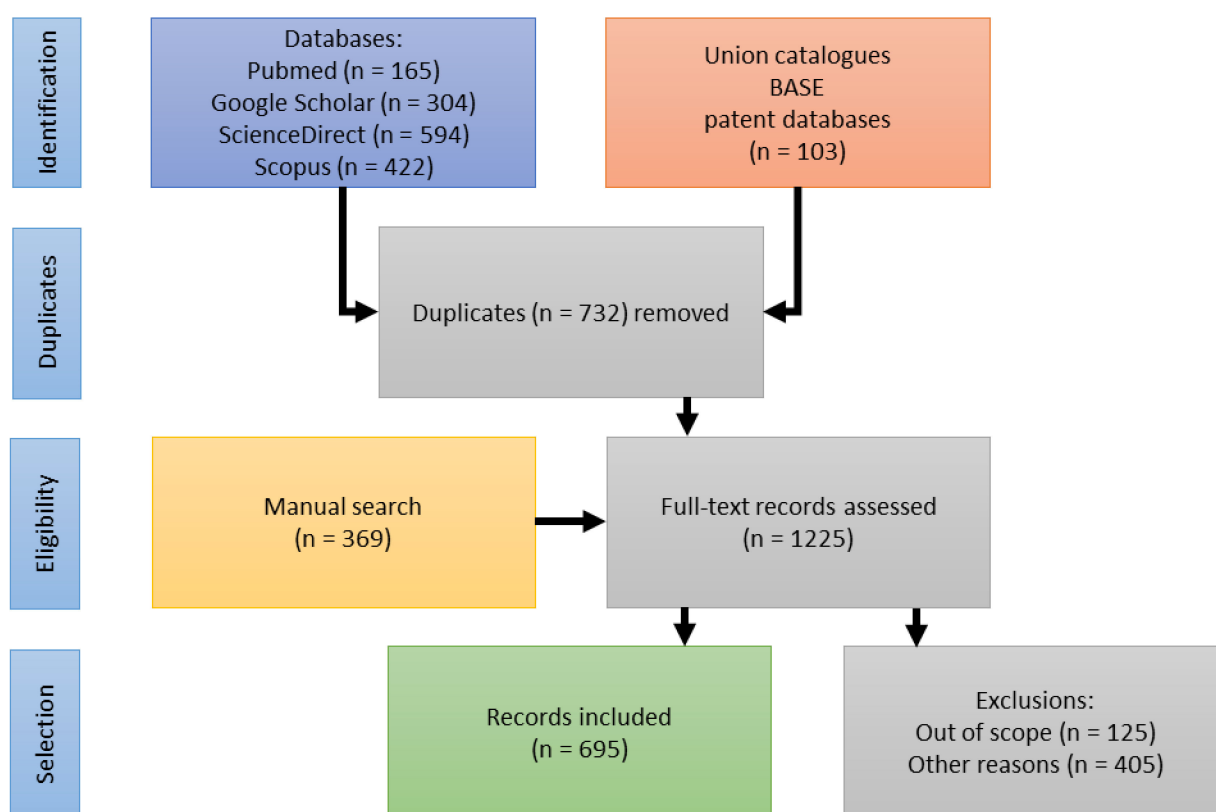


Figure 2. Flow diagram of the reference identification, screening and inclusion.

## 3. Nomenclature

### 3.1. Taxonomy

The genus *Harpagophytum* was first described as *Uncaria* Burch. by Burchell in his *Travels in the interior of southern Africa* (1822) [81]. However, he was apparently unaware that *Uncaria* had already been used by Schreber for a genus in the Rubiaceae in 1789.

Purportedly, de Candolle first noted this oversight, leading Meisner to describe the species as *Harpagophytum procumbens* DC [82]. However, de Candolle's section of the *Prodomus* was only published in 1845 [83], making Meisner the author of the genus and creating the following complete citation as:

*Harpagophytum* DC. ex Meisner, Pl. Vas. Gen. 1: 298 and 2: 206 (1840), syn.: *Uncaria* Burch., Trav. Int. S. Afr. 1:536 (1822), nom. illegit., non Schreb. 1789; type specimen: *Harpagophytum procumbens* (Burch.) DC. ex Meisner, Pl. Vas. Gen. 2:206 (1840); basionym: *Uncaria procumbens* Burch., Trav. Int. S. Afr. 1: 536 (1822).

Decaisne, in his review of the Pedalineae, attributed four distinct species to the genus: *H. procumbens* DC., *H. burchellii* Decne. (= *H. procumbens*), and for the first time, *H. zeyheri* and *H. leptocarpum* [*Uncaria leptocarpa* (Decne.) Ihlenf. & Straka] [84]. The genus was last reviewed by Ihlenfeldt and Hartmann (1970) [1], who differentiated two species and five subspecies primarily based on the shape of the fruit correlated with the number of seeds. They also provide the most recent botanical descriptions for all subspecies.

*Harpagophytum procumbens* (Burch.) DC. ex Meisn.:

- *H. procumbens* (Burch.) DC. ex Meisn. ssp. *procumbens*—(1).
- *H. procumbens* (Burch.) DC. ex Meisn. ssp. *transvaalense* Ihlenf. & H. Hartm.—(2).

*Harpagophytum zeyheri* Decne.:

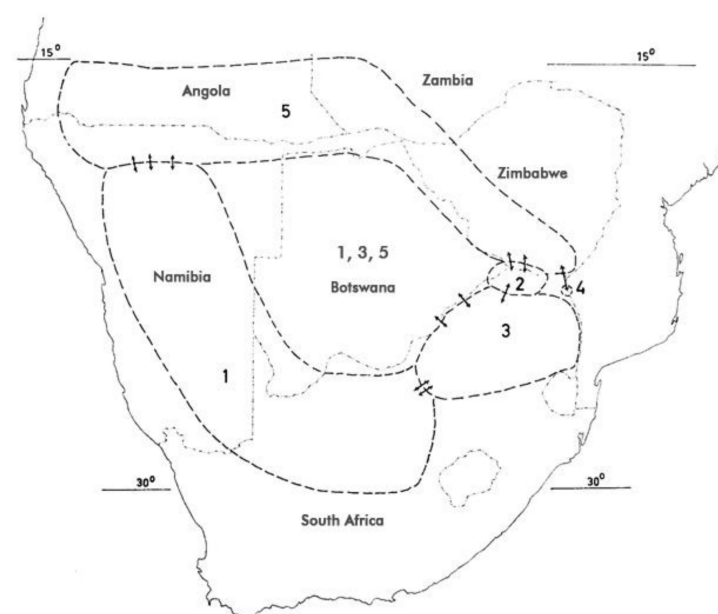
- *H. zeyheri* Decne. ssp. *zeyheri*—(3).
- *H. zeyheri* Decne. ssp. *schijffii* Ihlenf. & H. Hartm.—(4).
- *H. zeyheri* Decne. ssp. *sublobatum* (Engler) Ihlenf. & H. Hartm.—(5).

The numbers in parentheses represent the respective species in Figure 3 below.

Synonymy:

- *H. burchellii* Decne. = *H. procumbens* ssp. *procumbens* DC. ex Meisn.
- *H. zeyheri* f. *sublobatum* Engl. = *H. zeyheri* ssp. *sublobatum* (Engl.) Ihlenf. & H. Hartm.
- *H. procumbens* var. *sublobatum* (Engl.) Stapf = *H. zeyheri* ssp. *sublobatum* (Engl.) Ihlenf. & H. Hartm.
- *H. peglerae* Stapf = *H. zeyheri* ssp. *zeyheri* Decne.

Interspecific introgression has been described [85] and shown to be reflected in morphometric measurements, and DNA profiles. Both species and all their putative hybrids also showed geographical variation in biochemical composition [2,85–90].



**Figure 3.** Distribution of *H. procumbens* and *H. zeyheri* (after [1,64,91]). For numerical attribution of species, see Section 3.1. Arrows indicate introgression.

### 3.2. Vernacular Names

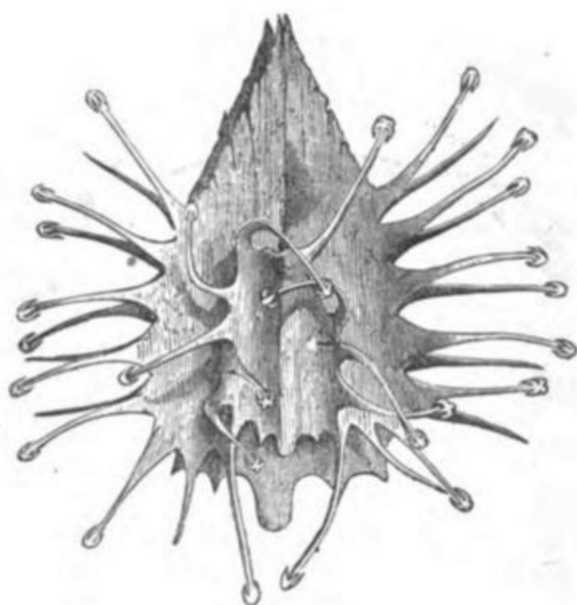
Teufelskralle, Trampelkette (Ger.); devil's claw, grapple plant (Eng.); garra-do-diabo (Port.); garra del diablo (Esp.); artiglio del diavolo (It.); griffe du diable (Fr.); sengaparile (Tswana), duiwelsklou, kloudoring, duiwelsdoring, sanddoring, beesdubbeltjie, wolspinnekop (Afr.); otjihatene (Oshihherero); //khuripe//khams, gamagu (Nama/Damara); elyata, omalyata (Oshikwanyama); ekatata, makakata (Oshindonga/Kwangali); likakata (Gciriku/Shambyu); !ao!ao, //xsamsa-//oro, //xemta≠'eisa (Kung); ǀam-si-ǀ q'oa-ka (West !Xoon), malamakwa (Silozi) [92–94].

### 4. Distribution

In the context of species interchangeability in commerce, it is noteworthy that the long-time assumption that only *H. procumbens* occurs in Namibia was disproved as early as the late 19th century. Ihlenfeldt discussed collections from the Etosha pan and later from the Kaokoveld and the Caprivi strip holding specimen of *H. zeyheri* [95]. Baum (1903) reported *H. procumbens* (Burch.) DC. var. *sublobatum* Engl. [= *H. zeyheri* Decne. ssp. *sublobatum* (Engler) Ihlenf. & H. Hartm.] from near lake Camelungo in southern Angola [96]. Cultivation has been experimented with in northern South Africa and, more recently, in Namibia, however, it has thus far neither proven very successful nor commercially viable [97–99].

### 5. Ethnobotany

Interestingly, there are no records for indigenous use of devil's claw until the beginning of the 20th century. Two accounts from the 19th century by Wood [100] and Cooke [101] (Figure 4) were the only ones that could be found making reference to devil's claw (as grapple plant—*Uncaria procumbens*) but focus on its “devilish nature”: “The reader may easily imagine the horrors of a bush which is beset with such weapons. No one who wears clothes has a chance of escape from them. If only one hooked thorn catches but his coat-sleeve, he is a prisoner at once. [ . . . ] If the reader would like to form an idea of the power of these thorns, he can do so by thrusting his arm into the middle of a thick rose-bush, and mentally multiplying the number of thorns by a hundred, and their size by fifty” [100].



**Figure 4.** Fruit of the “Grapnel” (note the misspelling!) plant from [101] vs. an actual fruit (photograph by the author).

Lübbert, in 1901, provided the first unambiguous account for the use of “Kuri-Khamiknollen” (= tubers of //khuripe//khams = *Harpagophytum*) in wound healing [102].



In 1907, Hellwig, medical officer of the imperial protection forces in German South-West Africa (Namibia), compiled a report on medicinal plant uses of the indigenous population, including an account of the Herero Samuel Kariko of the use of “otjihangatene” (= *Harpagophytum*) to treat cough, diarrhea, constipation, and venereal diseases [103]. Dinter, in 1909 and 1912 [104,105], utilized this report for his account of local food plants, but unfortunately omitted to include medicinal uses because he considered them unverified [106]. The fact that Hellwig provided an explicit source renders the colorful story of how the use of devil’s claw was “discovered” by Mehnert implausible and more likely part of a marketing strategy (see below) [107].

Later accounts corroborated these early records of traditional use of devil’s claw tubers primarily in the form of infusions and decoctions for digestive purposes, midwifery, pain relief, fever, diabetes, as a general tonic, for infectious diseases, and the dry powder topically as a wound dressing [40,92,108–112]. Ethnoveterinary uses in poultry have also been reported from Botswana [113]. It must be noted, however, that none of the early records clearly differentiate between species. It can only be speculated based on the origin of the records that Nama/Herero may have referred to *H. procumbens*, whereas reports from Botswana would concern mostly *H. zeyheri*.

## 6. Economy

### 6.1. History of Commercialization

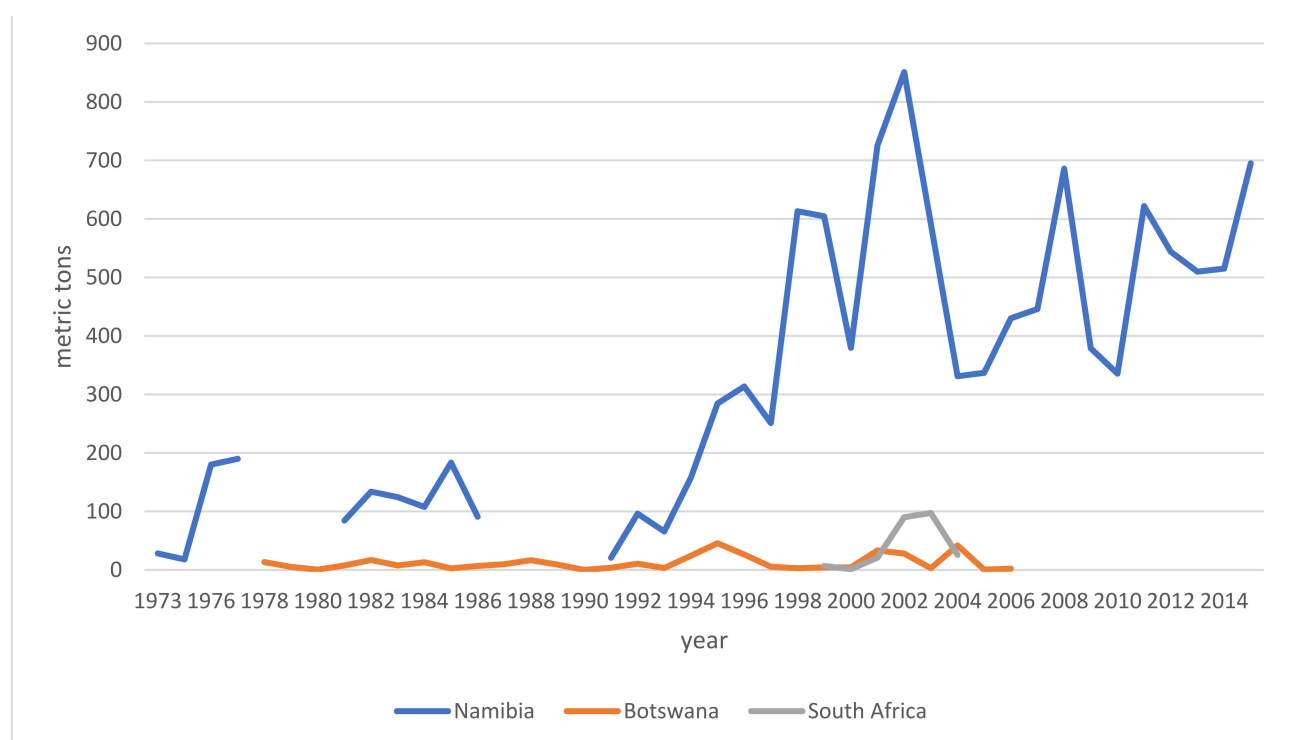
The story around how a soldier of the Kaiserliche Schutztruppe (German “imperial protection forces”) and later a farmer in Mariental (Namibia) Gottreich Hubertus Mehnert came across devil’s claw is firmly anchored in the scientific literature. Sometime during the so-called Hottentot uprising from 1904 to 1908 (in fact, a brutal war and genocide of the German troops primarily against the Herero and Nama tribes, which has most recently been recognized by the German government [114]), after observing a local healer successfully improving the condition of a gravely wounded local, he questioned the healer about the magic remedy, but the healer refused to disclose the place from where he had collected it. Purportedly, access to one of the most successful botanical drugs of modern times can be attributed to Mehnert’s pointer dog [107].

This version, however, must be relegated to the world of “romance” and seen as part of an elaborate marketing campaign—it is repeated in many slightly altered versions by multiple authors. Mehnert doubtlessly experimented with the root and found it effective in a variety of ailments, but the discovery of its medicinal powers ought to be attributed first and foremost to the native tribes and secondarily to Lübbert and Hellwig (see above) with whom they shared their knowledge. It was sheer luck that nobody else developed an interest, allowing Mehnert to consolidate his “research” and to commence commercialization. He eventually shared it, while being interned at camp Andalusia during the 2nd World War, with another “collateral” prisoner, German scientist O. H. Volk, who had visited German South-West Africa at the wrong time [115]. In the camp’s botanical society, knowledge was freely exchanged, which allowed Volk to return home to Germany with likely an entire laundry list of interesting plants. The introduction of devil’s claw (and probably also rooibos) to Germany can be attributed to him [58]. He shared his knowledge with Zorn who conducted some initial pharmacological research [116] and then initiated himself a flurry of investigations elucidating devil’s claw’s basic chemistry [117–128]. Meanwhile, in the early 1950s, Mehnert trademarked “Harpago” and started exporting to Germany. Erwin Hagen trademarked “Harpago” in Germany in the early 1960s and began to market it as an infusion and later in homoeopathic preparations [129] (Figure 5). “Harpagosan” tea was registered as a botanical drug in Germany in 1977 [130].

What follows is a story of extensive biochemical, pharmacological, toxicological, and clinical investigation, and the development of multiple standardized pharmaceuticals, initially in Germany (the German drug information system AMIce alone lists a total of 434 products, most of which, however, are no longer active, see, e.g., [131]), and since the 1980s, also in France and elsewhere [132]. Demand quickly started to grow exponentially, and concerns were raised over the sustainability of harvesting practices [133–135]. In response to unsustainable harvesting and poor processing practices, the Namibian Devil's Claw Exporter's Association Trust became part of a Good Agricultural and Collection Practice (GACP) project in which it intends to ensure that Namibian devil's claw is sustainably harvested and processed according to GACP guidelines.

## 6.2. Trade

Market demands impact livelihoods and policymakers alike. Trends indicate the health of an industry and inform resource assessments as well as regulatory interventions. With the following breakdown of trade and export data, I intend to address a controversy around species interchangeability, namely how the ingredient is regulated in the finished product markets. Hagen and others created a demand which local suppliers struggled to meet [133–135]. Sustainable collection and harvesting practices and governmental oversight were largely absent until ~1975. When originally only *H. procumbens* had been collected, driven by the economic boom, the collection and admixture of *H. zeyheri* commenced as early as the 1970s [11–14]. Furthermore, albeit on a much smaller scale than Namibia, both South Africa and Botswana [136–138] began to participate in the export market, also adding *H. zeyheri* into the supply chain (for distribution see above). Nott [14] and Taylor and Moss [138] broke down data specific to importing countries and explicitly listed importers, respectively. It is therefore safe to state that all importing markets have received either both species or mixtures thereof as early as the late 1970s. European regulators acknowledged the commercial reality by adding *H. zeyheri* to pharmacopeial monographs (see Section 6), while the US, for instance, remained oblivious to this practice, which stirred a controversy over the regulatory compliance and legitimacy of products containing *H. zeyheri* in 2015 [139]. The following overview of export volumes (Figure 6) is compiled from multiple sources [10,14,18,136–138,140–151] and further informed by the Namibian Ministry of Environment and Tourism (MET). The MET stopped sharing its data—based on export permits—with the public in 2015. According to one of the most prominent Namibian exporters of devil's claw, the years 2015–2020 saw a slight increase in demand, peaking in 2019 at around 1000 metric tons, otherwise averaging around 700 metric tons annually. Materials in trade (both species) fall into four categories: conventional (lowest) quality makes up about 80% of the trade volume, GACP quality currently contributes about 10–15% to the total, though efforts are underway to dramatically increase this proportion, certified organic quality adds organic certification to GACP-compliant material and makes up about 5–10% of the total trade volume, and finally, organic and Fair for Life certified material (*H. procumbens* only) contributes ~1% to the trade total. Prices per kg (for full container loads, cost and freight) range from €4.00 (*H. zeyheri*) and €6.70 (*H. procumbens*) for conventional quality, via €5.40 (*H. zeyheri*) and €8.20 (*H. procumbens*) for GACP quality, and €7.20 (*H. zeyheri*) and €8.50 (*H. procumbens*) for organic quality, to €9.00 for Fair for Life certified material (pers. comm. G. Diekmann, EcoSo Dynamics cc, Namibia). While these prices and volumes make this a sizeable industry, it must be noted that most of the value is of course added during the manufacture of pharmaceuticals in the target markets. It is also noteworthy that over all this time, Namibian exports may have been bolstered by (illegal) imports from Angola and Zambia, for which—naturally—no records exist [152].



**Figure 6.** Devil's claw exports by country—gaps reflect years in which no data was reported.

## 7. Representation in Pharmacopeias and Authoritative Compendia

Given its presence in the European marketplace since the 1950s and in the US at least since the late 1970s, pharmacopeial standards for devil's claw were set surprisingly late, likely due to suitable analytical methods not being available. While a qualitative assessment for the bitterness value according to the German Pharmacopoeia 7 (DAB 7) was suggested as early as 1977 [11], no specific monograph for devil's claw was included in DAB until 1993, which, in fact, required testing for harpagoside content (see Table 1 below). The first monograph in Europe appeared in the British Herbal Pharmacopoeia in 1981. Devil's claw first appeared in the European Pharmacopoeia in 1995, *H. zeyheri*, however, was not included as an allowable source species until 2003. The US Pharmacopeia, on the other hand, does not have a monograph for devil's claw other than a draft proposal published in the Herbal Medicines Compendium in 2013 [153].



**Table 1.** Representation of devil’s claw in pharmacopeias and authoritative compendia.

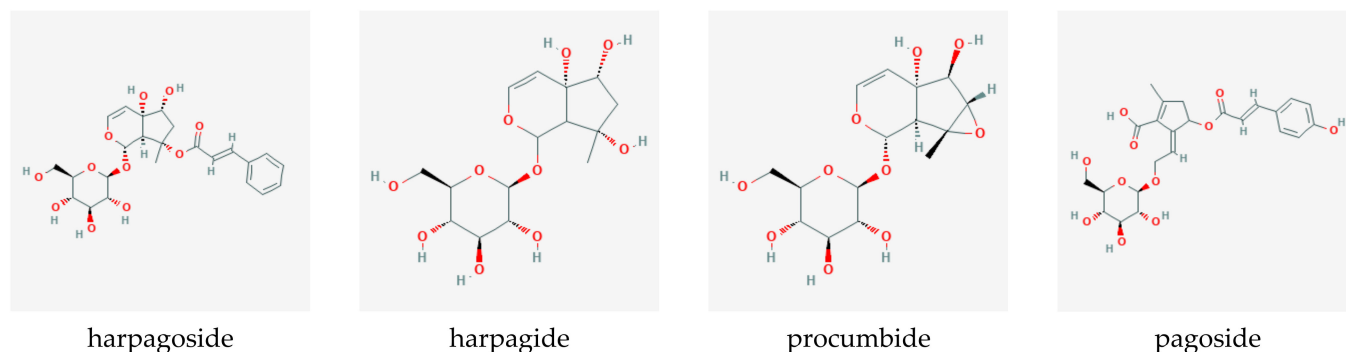
| Source                                    | Species Included                                                                            | Year | Reference    |
|-------------------------------------------|---------------------------------------------------------------------------------------------|------|--------------|
| <b>Official monographs</b>                |                                                                                             |      |              |
| British Herbal Pharmacopoeia              | <i>H. procumbens</i>                                                                        | 1981 | [154]        |
| Pharmacopée française                     | <i>H. procumbens</i>                                                                        | 1989 | [155]        |
| Kommission E                              | <i>H. procumbens</i> (corrected)<br>Monograph was informed by [65,156]                      | 1990 | [157]        |
| Pharmacopée française                     | <i>H. procumbens</i> dry extract                                                            | 1992 | [158]        |
| DAB 10 2nd. Supplement                    | <i>H. procumbens</i>                                                                        | 1993 | [159]        |
| European Pharmacopoeia 3rd ed.            | <i>H. procumbens</i>                                                                        | 1997 | [160]        |
| European Pharmacopoeia 4th ed. Suppl. 4.3 | <i>H. procumbens</i> / <i>H. zeyheri</i> (revised)                                          | 2003 | [161]        |
| Pharmacopée française                     | <i>H. procumbens</i> / <i>H. zeyheri</i><br>(homoeopathic preparations)                     | 2007 | [162]        |
| European Pharmacopoeia 7th ed.            | Devil’s claw dry extract                                                                    | 2008 | [163]        |
| Health Canada                             | <i>H. procumbens</i>                                                                        | 2008 | [164]        |
| European Pharmacopoeia 7th ed.            | <i>H. procumbens</i> / <i>H. zeyheri</i> (revised)                                          | 2011 | [165]        |
| Polish Pharmacopoeia 8                    | <i>H. procumbens</i> / <i>H. zeyheri</i>                                                    | 2008 | [166]        |
| USP Herbal Medicines Compendium           | <i>H. procumbens</i> / <i>H. zeyheri</i> (draft)                                            | 2013 | [153]        |
| European Medicines Agency (EMA)           | <i>H. procumbens</i> / <i>H. zeyheri</i> (revised from 2008)                                | 2016 | [15,167,168] |
| European Pharmacopoeia 9.6                | <i>H. procumbens</i> / <i>H. zeyheri</i> (revised)                                          | 2018 | [169]        |
| State Pharmacopoeia of Ukraine            | <i>H. procumbens</i> / <i>H. zeyheri</i>                                                    | 2018 | [170]        |
| Health Canada                             | <i>H. procumbens</i> / <i>H. zeyheri</i> (revised from 2008)                                | 2018 | [164]        |
| <b>Authoritative compendia</b>            |                                                                                             |      |              |
| ESCOP                                     | <i>H. procumbens</i>                                                                        | 1996 | [171]        |
| ESCOP                                     | <i>H. procumbens</i> (revised)<br>(omission of <i>H. zeyheri</i> is discussed in [172,173]) | 2003 | [16]         |
| World Health Organization                 | <i>H. procumbens</i>                                                                        | 2007 | [174]        |
| African Herbal Pharmacopoeia              | <i>H. procumbens</i>                                                                        | 2010 | [175]        |
| Martindale                                | <i>H. procumbens</i> (continuously revised from 1997)                                       | 2017 | [176]        |
| <b>Other compendia</b>                    |                                                                                             |      |              |
| Longwood Herbal Task Force                | <i>H. procumbens</i> / <i>H. zeyheri</i>                                                    | 1999 | [177]        |
| Herbal Medicines                          | <i>H. procumbens</i> / <i>H. zeyheri</i>                                                    | 2015 | [178]        |
| Phytopharmacy                             | <i>H. procumbens</i> / <i>H. zeyheri</i>                                                    | 2015 | [179]        |
| Kooperation Phytopharmaka                 | <i>H. procumbens</i>                                                                        | 2020 | [180]        |

## 8. Biochemistry

After Volk’s return to Germany (see Section 6.1) and following Zorn’s first pharmacological study of devil’s claw in 1958 [116], the university of Würzburg (Germany) became a research hotspot for the elucidation of active and suitable marker compounds in devil’s claw for decades to come. The effort was largely concluded by the end of the 1980s and comparatively little has been added to this effort since. Table 2 lists all publications focused on the biochemical composition. For analytical methods and quality control, see Section 9.

Iridoid-glycosides, primarily harpagoside, harpagide, and procumbide; phytosterols; phenylpropanoids such as verbascoside; triterpenes, such as oleanolic acid, 3 $\beta$ -acetyloleanolic acid, and ursolic acid; flavonoids, such as kaempferol and luteolin; unsaturated fatty acids,

cinnamomic acid, chlorogenic acid, and stachyose were identified as the most prominent compounds present in the root. Figure 7 shows the chemical structures of the primary iridoid glucosides present in *Harpagophytum* root.



**Figure 7.** Iridoid glucosides present in devil's claw root (source PubChem).

Interestingly, the biosynthetic pathway for harpagoside is not yet well-elucidated. The first step resulting in geranyl diphosphate is still considered to be under debate [17], since while the principal steps are known, some intermediates remain hypothetical and dependent on the “chosen” pathway. Georgiev and colleagues [30] propose two different routes to the formation of geranyl diphosphate from the condensation of dimethylallyl diphosphate and isopentenyl diphosphate, the latter being supplied through either the mevalonate or the mevalonate-independent pathways. Geraniol is synthesized by geraniol diphosphate synthase and hydroxylated to form 8-hydroxygeraniol, followed by two oxidation steps and isomerization into 8-epi-iridodial. Carboxylation and glycosylation form its glycoside, which, in turn, is transformed into harpagide through decarboxylation and oxidations. Finally, harpagoside emerges as the product of cinnamoyl esterification at the 3-hydroxyl position.

Several studies have investigated differences in the quantitative composition of different *Harpagophytum* species, subspecies, and hybrids [19,181–184], and found the composition to be highly variable, depending on the material used, collection location, natural variation within the taxa, environmental influences, processing, and analytical methods. Content of the marker compound harpagoside is generally lower in *H. zeyheri* and has been found to be between 0%, 1%, and 4% in *H. procumbens* and between 0% and 3% in *H. zeyheri*. Verbascoside and isoverbascoside contents in *H. procumbens* varied between 0.2% and 0.4% and 0.2% and 1%, respectively. Pagoside content in *H. procumbens* varied between 0.06% and 0.16%. Hybrids showed the highest contents for most key compounds except harpagoside. 8-p-Coumaroylharpagide content in *H. zeyheri* varies between 0.7% and 1.4%, while being effectively absent in *H. procumbens*. The lower harpagoside content in *H. zeyheri* has in the past driven controversies over species equivalence in terms of clinical efficacy, however, this debate seems futile as a marker compound is not necessarily the (only) active one. Indeed, the pre-clinical research (outlined in Section 10) indicates that activities of multiple rather than single compounds may contribute to the overall effect.

**Table 2.** Elucidation of the biochemical composition of devil's claw root.

| Topic                                                                                    | Year | Reference |
|------------------------------------------------------------------------------------------|------|-----------|
| Isolation and characterization of harpagoside                                            | 1960 | [117]     |
| Stachyose, raffinose, and a further glucoside in the aqueous phase                       | 1961 | [118]     |
| Characterization of harpagoside                                                          | 1961 | [119]     |
| Isolation and characterization of harpagoside and harpagide                              | 1962 | [120]     |
| Characterization of harpagoside                                                          | 1962 | [121]     |
| Characterization of harpagide                                                            | 1963 | [122]     |
| Isolation of stachyose and a further glucoside                                           | 1963 | [123]     |
| Characterization of harpagoside                                                          | 1964 | [124]     |
| Isolation of procumbide                                                                  | 1964 | [125]     |
| Structural characterization of harpagoside                                               | 1966 | [126]     |
| Characterization of procumbide and further constituents                                  | 1967 | [127]     |
| Characterization of procumbide                                                           | 1968 | [128]     |
| Characterization of a chinone and other constituents                                     | 1970 | [185]     |
| Characterization of procumbide                                                           | 1971 | [186]     |
| Further constituents                                                                     | 1974 | [187]     |
| Elucidation of triterpene esters                                                         | 1975 | [188]     |
| Overview of known mono-, di-, and sesquiterpenoids with pharmacological activity         | 1977 | [189]     |
| Elucidation of a resin, an essential oil, and a mucilaginous fraction                    | 1978 | [190]     |
| Structural characterization of procumbide                                                | 1979 | [191]     |
| Glucose, galactose, fructose, myo-inositol, sucrose, raffinose, and stachyose identified | 1979 | [192]     |
| Preparation and structure of harpagogenine                                               | 1981 | [193]     |
| Carbohydrates and harpagoside in tissue cultures and roots of devil's claw               | 1982 | [194]     |
| New iridoids: 8-O-(p-coumaryl)-harpagide and procumboside                                | 1983 | [195]     |
| Novel iridoid and phenolic compounds                                                     | 1987 | [196]     |
| Three pyridine monoterpene alkaloids from harpagoside and commercial extract             | 1999 | [197]     |
| Review of iridoids                                                                       | 2000 | [198]     |
| Review of composition (both species)                                                     | 2002 | [199]     |
| Two diterpenes, (+)-8,11,13-totaratriene-12,13-diol and ferruginol                       | 2002 | [200]     |
| New iridoid- and phenylethanoid glycosides                                               | 2003 | [201]     |
| Acetylated phenolic glycosides                                                           | 2003 | [202]     |
| Pharmacological characterization of harpagoside                                          | 2004 | [203]     |
| Chinane-type tricyclic diterpenes and other minor compounds                              | 2006 | [204,205] |
| Review of iridoids and other compounds                                                   | 2006 | [206,207] |
| Review of chemical constituents                                                          | 2007 | [208]     |
| Elucidation and characterization of compounds with specific pharmacologic profiles       | 2008 | [209,210] |
| New triterpenoid glycoside, harproside, and new iridoid glycoside, pagide                | 2010 | [211]     |
| Kynurenic acid content                                                                   | 2013 | [212]     |
| New iridoid diglucoside                                                                  | 2016 | [213]     |

### 9. Analytical Methods and Quality Control

The quickly increasing popularity of devil's claw products required an ongoing effort to develop and refine tools to identify and quantify devil's claw in its raw, processed, and finished product states. Initially, the primary aims were identification and contaminants [214,215], later, standardization [11] and quality control [216,217], and finally identification and quantification methods to support pharmacological and clinical research. Early methods, however, did not account for species differentiation, i.e., simple pharmacy-proof methods of the 1970s would likely not have been able to differentiate between *H. procumbens* and *H. zeyheri*. In fact, methods and equipment refined enough to do so, regardless of the extent of processing, only became available in the 1990s. Analysis of retention samples retrospectively determined the presence of both species in commercial products. Table 3 provides a quick reference to publications of methods of quality control in chronological order. In current practice, the most commonly used methods for identification and assaying devil's claw raw materials and products include TLC, HPLC, HTPLC, and LC/MS, for instance, the current edition of the European Pharmacopoeia employs microscopy and TLC for identification and LC for harpagoside quantification; more recently, chemometric modeling and hyperspectral imaging have emerged as promising methods for species differentiation.

**Table 3.** Analytical methods and methods of quality control.

| Topic                                                                                                                                                                  | Year | Reference |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|-----------|
| Macroscopic and microscopic descriptions                                                                                                                               | 1964 | [58]      |
| Macroscopic, microscopic, and chromatographic differentiation of commercial drug samples                                                                               | 1973 | [218]     |
| Macroscopic, microscopic, and chromatographic differentiation of commercial drug samples                                                                               | 1974 | [219]     |
| Simple TLC with <i>Scrophularia nodosa</i> as a reference standard                                                                                                     | 1975 | [220]     |
| Distribution of harpagoside within <i>H. procumbens</i> and <i>H. zeyheri</i>                                                                                          | 1977 | [221]     |
| Standardization by determination of harpagoside, bitterness value, and dry residue                                                                                     | 1977 | [11]      |
| Spectrometric method for the quantitative evaluation of the glycoiridoids                                                                                              | 1978 | [222]     |
| Report of falsified, adulterated, and contaminated commercial products                                                                                                 | 1978 | [214]     |
| Quantitative determination of harpagoside via HPLC                                                                                                                     | 1980 | [223]     |
| GLC method for the determination of harpagide and harpagoside                                                                                                          | 1981 | [224]     |
| Histological characteristics under scanning electron microscope                                                                                                        | 1984 | [225]     |
| Stability of iridoids during extraction                                                                                                                                | 1985 | [226]     |
| Determination of harpagoside, luteolin, chlorogenic, caffeic, and cinnamic acid from extracts                                                                          | 1986 | [227]     |
| Analysis of permethylated iridoid glycosides by GC/MS                                                                                                                  | 1986 | [228]     |
| Determination of harpagide, 8-p-coumaroyl harpagide (8-PCHG), and harpagoside by HPLC                                                                                  | 1994 | [229]     |
| Analysis of the harpagoside content of commercial samples by HPLC                                                                                                      | 1995 | [230]     |
| TLC method for determination of harpagoside                                                                                                                            | 1995 | [231]     |
| HPLC/UV for the determination of harpagoside in commercial powdered dry extracts                                                                                       | 1996 | [232]     |
| HPLC/UV for the determination of harpagoside in commercial tea products                                                                                                | 1996 | [233]     |
| HPLC/UV for the determination of harpagoside in commercial products (multiple dosage forms)                                                                            | 1996 | [234]     |
| HTPLC for quantitative determination of harpagoside                                                                                                                    | 1996 | [235]     |
| HPLC determination of harpagide, 8-PCHG, and harpagoside in <i>H. procumbens</i> and <i>H. zeyheri</i> —ratio of harpagoside/8-PCHG can be used to distinguish species | 1997 | [19]      |
| HPLC determination of ratio of harpagoside/8-PCHG, 8-PCHG < 8% proposed for <i>H. procumbens</i>                                                                       | 1998 | [12]      |
| Methods for quality control and stability testing of <i>Harpagophytum</i> homeopathic preparations                                                                     | 1998 | [236]     |
| HPLC/UV for the determination of harpagoside in commercial dry extract products                                                                                        | 1999 | [237]     |

Table 3. Cont.

| Topic                                                                                                                                            | Year | Reference |
|--------------------------------------------------------------------------------------------------------------------------------------------------|------|-----------|
| Differentiation of <i>H. procumbens</i> (<9% 8-PCHG), mixtures (10–30% 8-PCHG), and <i>H. zeyheri</i> (>31 8-PCHG) proposed                      | 2000 | [13]      |
| Biopharmaceutical quality, release of active ingredients in vitro, and disintegration tests                                                      | 2000 | [238]     |
| Methods for detection of adulterations and contaminations                                                                                        | 2001 | [239]     |
| Bioequivalence of <i>Harpagophytum</i> products                                                                                                  | 2002 | [240]     |
| Near infrared spectroscopy (NIRS) determination of harpagoside, 8-PCHG, and their ratio                                                          | 2003 | [241]     |
| NIR-FT-Raman spectroscopy for identification and quantification of harpagoside                                                                   | 2005 | [242]     |
| Determination of harpagoside from CO <sub>2</sub> -extracts with HPLC and HPTLC-densitometry                                                     | 2005 | [243]     |
| NIRS determination of harpagoside, 8-PCHG, and their ratio                                                                                       | 2005 | [244]     |
| Fast HPLC determination of harpagoside using a monolithic silica column                                                                          | 2005 | [245]     |
| Validation of a fast-HPLC for separation of iridoid glycosides to distinguish between species                                                    | 2005 | [246]     |
| LC-DAD-MS/SPE-NMR hyphenation for identification of isobaric iridoid glycoside regioisomers                                                      | 2005 | [247]     |
| X-ray fluorescence spectrometry (SRTXRF) to determine trace elements                                                                             | 2005 | [248]     |
| Determination of aflatoxin B <sub>1</sub>                                                                                                        | 2006 | [249]     |
| LC/MS determination of harpagoside, 8-PCHG, and their ratio                                                                                      | 2006 | [250]     |
| Computational study to estimate the proton and sodium cation affinities of harpagide                                                             | 2006 | [251]     |
| Quality parameters of finished products in the German market                                                                                     | 2006 | [252]     |
| Proposal to revise the drug–extract ratio of aqueous/ethanolic extracts                                                                          | 2006 | [253]     |
| Methods for determination of minerals and heavy metals                                                                                           | 2007 | [254]     |
| Analysis of iridoids in horse urine                                                                                                              | 2008 | [255]     |
| Solid-phase extraction for LC/MS analysis of harpagoside, 8-PCHG, and harpagide in equine plasma                                                 | 2008 | [256]     |
| Validated HPTLC method for the determination of harpagoside                                                                                      | 2008 | [257]     |
| High-Pressure Liquid Chromatography-Diode Array Detection (HPLC-DAD) for harpagoside and isoacteoside contents                                   | 2009 | [258]     |
| HPLC-DAD and HPLC–ESI-MS analyses of stability of the constituents                                                                               | 2011 | [181]     |
| Anatomical study of secondary tubers and quantification of harpagoside by HPLC                                                                   | 2012 | [259]     |
| Authenticity and contamination tests by DNA barcoding                                                                                            | 2013 | [260]     |
| Exploring species substitution through chemometric modeling of <sup>1</sup> H-NMR and UHPLC-MS                                                   | 2014 | [182]     |
| Mid-infrared spectroscopy and short-wave infrared hyperspectral imaging for qualitative assessment of <i>H. procumbens</i> and <i>H. zeyheri</i> | 2014 | [85,88]   |
| Morphology, histochemistry, and ultrastructure of foliar mucilage-producing trichomes                                                            | 2014 | [261]     |
| NMR-based chemometric approach for species differentiation                                                                                       | 2014 | [262]     |
| UPLC Q-TOF ESI determination of harpagosides in <i>H. procumbens</i> , <i>H. zeyheri</i> , and extracts                                          | 2016 | [263]     |
| Loss on drying and total ash                                                                                                                     | 2016 | [264]     |
| Comparison of microwave and ultrasound-assisted with conventional solvent extraction methods for harpagoside determination                       | 2016 | [265]     |
| Innovative micro-extraction techniques to determine harpagoside and phenolic patterns in <i>H. procumbens</i> and finished products              | 2017 | [266]     |
| Determination of suitable extraction solvent                                                                                                     | 2017 | [267]     |
| GC-MS determination of chemical constituents                                                                                                     | 2017 | [268]     |
| DNA barcoding to detect contamination and substitution                                                                                           | 2017 | [269]     |
| HPLC and MS analyses of spagyric tinctures                                                                                                       | 2019 | [270]     |



Table 3. Cont.

| Topic                                                                                            | Year | Reference |
|--------------------------------------------------------------------------------------------------|------|-----------|
| Validated RP-HPLC-PDA method for quantification of harpagoside in extracts and finished products | 2019 | [271]     |
| UPLC–MS profiling of samples from different locations                                            | 2019 | [90]      |
| Determination of macro- and micro-elements in finished products using ICP OES                    | 2020 | [272]     |
| HPLC method for harpagoside determination in finished product (tablet)                           | 2020 | [273]     |

### 10. Processing, Products, Applications

The majority of data on processing and delivery systems is provided in the list of patents compiled in Section 14. EMA's HMPC assessment report on *H. procumbens* and/or *H. zeyheri*, radix, provides an overview of extracts that are most commonly used in commercial products [167]:

- Liquid extract (1:1; 30% *v/v* ethanol)
- Soft extract (2.5–4.0:1; 70% *v/v* ethanol)
- Dry extract (1.5–2.5:1; water)
- Dry extract (5–10:1; water)
- Dry extract (2.6–4:1; 30% *v/v* ethanol)
- Dry extract (1.5–2.1:1; 40% *v/v* ethanol)
- Dry extract (3–5:1; 60% *v/v* ethanol)
- Dry extract (3–6:1; 80% *v/v* ethanol)
- Dry extract (6–12:1; 90% *v/v* ethanol)
- Tincture (1:5), extraction solvent ethanol 25% (*v/v*)

Figure 8 shows the processing from harvest to the raw material in commerce. Historically, teas [67,274], e.g., Harpagosan (see above), fluidextracts [42,67], spray-dried aqueous extract [26,67], homeopathic preparations for both oral (p.o.) and intraperitoneal (i.p.) application [26,27,67], and powder in capsules [26,67,93] were also common galenic forms. The European Pharmacopoeia stipulates a minimum of 1.2% of harpagoside in the raw material [169]. Dry extracts were standardized to contain a minimum of 1.5% m/m of harpagoside [167].

More recently, Plaizier-Vercammen and Bruwier evaluated the impact of excipients on friability and hygroscopicity of direct compression of a spray-dried *Harpagophytum* extract [275]. Günther et al. analyzed the parameters affecting supercritical fluid extraction with CO<sub>2</sub> of harpagoside [276]. Performance of a topical preparation with devil's claw extract on acrylic acid polymers base compared to ketoprofen was assessed by Piechota-Urbanska and colleagues [277]. Both formulations demonstrated rheological stability and high pharmaceutical availability. Almajdoub described a freeze-dried aqueous extract of *H. procumbens* encapsulated in lipid vesicles by using a dry film hydration technique with and without further alginate coating for optimal (delayed) release and small intestine absorption [278]. Development of a gastro-resistant coated tablet prepared from a standardized hydroethanolic root extract for the purpose of more effective delivery and consequent dose reduction was reported by Lopes et al. [279].



**Figure 8.** Clockwise: *H. procumbens*, secondary tubers, drying of the sliced tubers, article of commerce (photographs by the author). The article of commerce shown here is conventional quality (see Section 6). Note the difference in color of the slices shown on the bottom right, which were harvested and processed in compliance with GACP.

## 11. Pre-Clinical Research

### 11.1. Pharmacology

Studies mainly investigated anti-inflammatory activities and were conducted with various extracts, extract fractions, or isolated compounds. *Harpagophytum* iridoid compounds are considered the primary actives, to which anti-inflammatory, antinociceptive, analgesic, antimicrobial, chemopreventive, hepatoprotective, neuroprotective, and immunomodulatory effects are commonly attributed [189,198,209,280,281]. As cyclooxygenase (COX)-1/2 inhibitors have emerged as important targets for treating rheumatoid arthritis, the influence on the arachidonic acid pathway has been a research focus. The most commonly used methods for measuring peripheral analgesic activity were the various forms of the writhing tests, hot-plate test, and the Randall–Selitto test in rats and mice. To demonstrate anti-inflammatory effects, different animal models of inflammation were commonly used, e.g., the carrageenan-induced mouse/rat paw edema, the 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced mouse edema, the granuloma pouch test, zymosan-induced arthritis, albumin-induced rat paw edema, adjuvant-induced arthritis in rats (*M. tuberculosis*; Freund adjuvant), and Adriamycin-induced rat paw edema. More advanced in vivo and a variety of in vitro and ex vivo models were developed and employed over time (see Tables 4–7 below).

**Table 4.** In Vitro experiments regarding analgesic/antinociceptive and anti-inflammatory effects of devil's claw preparations and compounds.

| Study                                                                                                                                                                                                                                                                                                                                                             | Year       | Reference                                                        |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|------------------------------------------------------------------|
| Guineapig isolated ileum; harpagoside (40 µg/mL) and harpagogenine (2.5 µg/mL) non-selectively inhibited contractions; harpagide (40 µg/mL) increased the cholinergic response without inhibitory effects.                                                                                                                                                        | 1981       | Fontaine et al. [282]                                            |
| Calcium ionophore-stimulated mouse peritoneal macrophages; harpagoside and harpagide inhibited leukotriene C4 (LTC4) and prostaglandin E2 (PGE2) release (not significant) and harpagoside inhibited thromboxane B2 (TXB2) release, similar to ibuprofen.                                                                                                         | 2000       | Benito et al. [283]                                              |
| Lipopolysaccharide-stimulated primary human monocytes; <i>Harpagophytum</i> * extract, harpagoside, and harpagide extract prevented synthesis of tumor necrosis factor alpha (TNF-α), isolated substances showed no effect.                                                                                                                                       | 2001       | Fiebich et al. [284]                                             |
| Ionophore A23187 stimulated Cys-LT levels in anticoagulated whole blood; <i>Harpagophytum</i> extract, harpagoside, and extract fractions; inhibitory effect stronger with extract than harpagoside, no effect with fractions without harpagoside, suggesting relation between serum harpagoside and inhibition of leukotriene biosynthesis.                      | 2001       | Loew et al. [285]                                                |
| Modified Hens-Egg-Test at the Chorion-Allantoin-Membrane (HET-CAM) and lipoxygenase assay; ethanolic extracts of <i>Harpagophytum</i> (60%, 30%, 0%); 30% most potent in HET-CAM, 60% most potent in inhibiting lipoxygenase pathway.                                                                                                                             | 2002       | Wahrendorf et al. [286]                                          |
| Human neutrophil elastase (HNE); <i>Harpagophytum</i> extract, fractions, and isolates; weak dose-dependent inhibition was observed, with <i>H. procumbens</i> extract twice as strong as <i>H. zeyheri</i> ; 6'-O-acetyl-acteoside (not in <i>H. procumbens</i> ) the strongest isolate, followed by isoacteoside and pagoside (dominant in <i>H. zeyheri</i> ). | 2002, 2003 | Boje [199]; Boje et al. [201]                                    |
| Lipopolysaccharide (LPS)-induced inflammation in mouse fibroblast cell line L929; 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, reverse transcription-polymerase chain reaction, PGE2 immunoassay, and nitric oxide (NO) detection; aqueous <i>H. procumbens</i> extract; suppression of PGE2 synthesis and NO production.            | 2003       | Jang et al. [287]                                                |
| Human chondrocytes stimulated with interleukin (IL)-1β; <i>Harpagophytum</i> dry extract (210, 480 mg); immunofluorescence and Western blot analyses showed dose-dependent suppression of matrix metalloproteinases production via inhibition of cytokine expression.                                                                                             | 2004       | Schulze-Tanzil et al. [288]                                      |
| Bovine and human chondrocytes, stimulated with LPS and IL-1β, respectively; <i>Harpagophytum</i> extracts (100, 33, 1 µg/mL); significant suppression of PGE2 expression and NO synthase in human chondrocytes (bovine experiment was flawed).                                                                                                                    | 2006       | Chrubasik [289], Chrubasik et al. [290], Hadzhiyski et al. [291] |
| Human whole-blood assay, human polymorph nuclear leucocytes (PMNL) assay; COX-2, 5-lipoxygenase (LOX) inhibition, respectively; comparison of <i>Harpagophytum</i> aqueous-ethanolic and CO2 extracts (2%, 20%, and 30% harpagoside, respectively); variable but weak PGE2 inhibition for all, superiority of CO2 extracts in 5-LOX inhibition.                   | 2006       | Günther et al. [292]                                             |
| Human HepG2 hepatocarcinoma and RAW 264.7 macrophage cell lines; harpagoside (0.1–200 µM); LPS-induced mRNA, COX-2 expression, and inducible nitric oxide (iNOS) inhibited, and NF-κB activation suppressed.                                                                                                                                                      | 2006       | Huang et al. [293]                                               |
| LPS-stimulated THP-1 cells; incubated with 50 µg/mL <i>H. procumbens</i> dry extract (DER 1.5–3); microarray (gene chip) assay; noted inhibition of several inflammatory targets.                                                                                                                                                                                 | 2009       | Balthazar et al. [294]                                           |
| COX-2 (ovine) enzyme, stimulated by arachidonic acid and TMPD; <i>H. procumbens</i> extract, harpagoside, and harpagide; direct inhibition (68%) of COX-2, harpagoside, and harpagide contributed 1.5% and 13%, respectively.                                                                                                                                     | 2011       | Ebrahim and Uebel [295]                                          |

Table 4. Cont.

| Study                                                                                                                                                                                                                                                                                                                                                                                                | Year | Reference               |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|-------------------------|
| Isolated murine macrophages; <i>H. procumbens</i> crude methanolic extract, harpagoside, phenylethanoid-containing fraction, verbascoside; strong inhibitory action related to NO and TNF- $\alpha$ and IL-6 production, and COX-1 and COX-2 expression, comparable to harpagoside.                                                                                                                  | 2011 | Gyurkovska et al. [296] |
| LPS-stimulated human monocytes and mouse RAW264.7 macrophages; molecular targets; <i>H. procumbens</i> ethanolic extract (2.9% harpagoside); dose-dependent inhibition of TNF- $\alpha$ , IL-6, IL-1 $\beta$ , PGE2, and COX-2, inhibition of activator protein (AP)-1 pathway without affecting NF- $\kappa$ B and mitogen-activated protein (MAP) kinase pathways.                                 | 2012 | Fiebich et al. [297]    |
| Pre-transdermal and post-transdermal COX-2 inhibition and permeation studies; <i>H. procumbens</i> extract, harpagoside, harpagide; hydroxypropyl cellulose gels (carrier) with permeation enhancers tested on synthetic membranes, with and without enhancers on human skin, Azone <sup>®</sup> enhancer chosen, direct COX-2 inhibition maintained (pre-permeation 80%, post-permeation 77% COX-2) | 2013 | Ebrahim [298]           |
| LPS-stimulated monocytic THP-1 cells; enzyme-linked immunosorbent assays, WST-1 assay; <i>Harpagophytum</i> extract; dose-dependent suppression of TNF- $\alpha$ , IL-6, IL-8, independent from external metabolic activation.                                                                                                                                                                       | 2014 | Hostanka et al. [299]   |
| Primary human osteoarthritis chondrocytes; harpagoside (600 $\mu$ M); significant reduction in IL-1 $\beta$ -induced expression of IL-6, no effect on nuclear levels of NF- $\kappa$ B.                                                                                                                                                                                                              | 2015 | Haseeb et al. [300,301] |
| Differentiated 3T3-L1 adipocytes; harpagoside; activation of peroxisome proliferator-activated receptor (PPAR)- $\gamma$ , significant inhibition of TNF- $\alpha$ -induced mRNA synthesis and production of atherogenic adipokines including IL-6, plasminogen activator inhibitor-1, and monocyte chemoattractant protein-1.                                                                       | 2015 | Kim et al. [302]        |
| IFN- $\gamma$ /LPS-stimulated THP-1 cells; harpagoside and harpagide; decreased TNF- $\alpha$ -secretion in PMA-differentiated THP-1 cells, positive effect on TNF- $\alpha$ and intercellular adhesion molecule-1 mRNA-expression in undifferentiated cells.                                                                                                                                        | 2016 | Schopohl et al. [303]   |
| Human synovial membranes from subjects with and without osteoarthritis; <i>H. procumbens</i> extract, multiple solvents; cannabinoid type 2 (CB2) receptor enhanced, phosphatidylinositol-specific phospholipase C $\beta$ 2 downregulated with water and DMSO, fatty acid amide hydrolase (FAAH) activity inhibited with all.                                                                       | 2020 | Mariano et al. [304]    |

\* Species not specified; however, all specific attribution must be cautioned against due to the frequent admixture.

**Table 5.** In Vivo experiments regarding analgesic/antinociceptive and anti-inflammatory effects of devil's claw preparations and compounds.

| Study                                                                                                                                                                                                                                                 | Year | Reference               |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|-------------------------|
| Formaldehyde-induced arthritis in rats; <i>Harpagophytum</i> * infusion p.o. and subcutaneous; significant reduction of swelling, subcutaneous application better tolerated.                                                                          | 1958 | Zorn [116]              |
| Albumin-induced paw edema, granuloma-pouch-test, formaldehyde-induced arthritis in rats, rabbit ear-withdrawal test; whole extract and harpagoside, intravenous (i.v.) and i.p.; some (significant) effects shown similar to those of phenylbutazone. | 1970 | Eichler and Koch [305]  |
| Rats; blood panel; <i>Harpagophytum</i> aqueous extract 3:1, 30 mg/kg; triglycerides, uric acid, urea, and cholesterol significantly reduced.                                                                                                         | 1974 | Int. Bio Research [306] |
| Dextran-induced paw edema; rats; <i>Harpagophytum</i> , aqueous extract 3:1; edema significantly reduced.                                                                                                                                             | 1974 | Int. Bio Research [307] |



Table 5. Cont.

| Study                                                                                                                                                                                                                                                                                                                                        | Year | Reference                                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|------------------------------------------|
| Eight <i>Harpagophytum</i> dry extracts, p.o. and i.v., tested for analgesic and antiphlogistic effects in five animal models; some analgesic and antiphlogistic effects with methanolic, butanolic, and fluid extracts; pure harpagoside superior, semi-chronic models showed better results.                                               | 1978 | Erdös et al. [308]                       |
| Carrageenan-induced rat paw edema (30) and adjuvant-induced arthritis in rats (40); <i>Harpagophytum</i> 100–1000 mg/kg, single dose and 21 days; no significant effect in the edema model, some effect in the arthritis model at the higher dose.                                                                                           | 1979 | McLeod et al. [309]                      |
| Carrageenan-induced rat paw edema; aqueous ethanolic crude extract of <i>Harpagophytum</i> and various fractions; only crude extract effective, concludes that harpagoside is likely not the (only) active.                                                                                                                                  | 1986 | Duband [274]                             |
| Carrageenan-induced rat paw edema; methanolic extract of <i>Harpagophytum</i> ; dose-dependent edema inhibition.                                                                                                                                                                                                                             | 1990 | Máñez et al. [310]                       |
| Carrageenan-induced rat paw edema; aqueous extract of <i>Harpagophytum</i> (1.8% harpagoside) and harpagoside i.p.; significant reduction of edema with extract, not with harpagoside.                                                                                                                                                       | 1992 | Lanthers et al. [311]                    |
| Adriamycin-induced rat paw edema; <i>Harpagophytum</i> , 37, 370, and 3700 mg/kg; dose-dependent edema inhibition up to 48% after one hour; compared to control (Adriamycin only) effect transient after 5 days.                                                                                                                             | 1992 | Jadot and Lecomte [312]                  |
| Carrageenan-induced mouse paw edema and TPA-induced mouse ear edema; harpagoside (p.o. and topically); no notable protective effects.                                                                                                                                                                                                        | 1994 | Del Carmen Recio et al. [313]            |
| Carrageenan-induced rat paw edema; aqueous extracts of <i>Harpagophytum</i> (400 and 800 mg/kg, 2.72% harpagoside) i.p. pre-treatment, p.o., and intraduodenally; significant inhibition i.p. and intraduodenally, no effect orally.                                                                                                         | 1994 | Soulimani et al. [314]                   |
| Carrageenan-induced mouse paw edema; <i>Harpagophytum</i> and <i>Uncaria tomentosa</i> extracts; no effect on inflammatory response individually, but significant effect combined.                                                                                                                                                           | 2002 | Abe et al. [315]                         |
| Freund's adjuvant-induced arthritis in rats; acute (25, 50, or 100 mg/kg) or chronic (100 mg/kg) treatments with <i>H. procumbens</i> solution; increased 'latency of paws' withdrawal and reduction in paw edema, compared to control.                                                                                                      | 2004 | Andersen et al. [316]                    |
| Fresh egg albumin-induced pedal edema in rats, hot-plate and acetic acid tests in mice; <i>H. procumbens</i> root aqueous extract (50–800 mg/kg i.p.); significant effect against nociceptive pain stimuli and significant, dose-dependent reduction of edema.                                                                               | 2004 | Mahomed and Ojewole [317], Mahomed [318] |
| Carrageenan-induced back-paw edema, Freund's adjuvant-induced arthritis, cotton pellet-induced granuloma, and writhing tests in rats and mice; <i>Harpagophytum</i> aqueous extract (800 mg/kg bw), acetyl salicylic acid and indomethacin as controls; significant effects in all models similar to indomethacin and acetyl salicylic acid. | 2005 | Ahmed et al. [319]                       |
| TPA-induced COX-2 expression in mouse skin; <i>Harpagophytum</i> methanolic extract (200, 400 µg) topically prior to TPA application; significant inhibition of COX-2 expression, COX-1 unchanged, no effect on NF-κB.                                                                                                                       | 2005 | Kundu et al. [320]                       |
| Carrageenan-induced back-paw edema in rats; <i>H. procumbens</i> extract (100, 200, 400, or 800 mg/kg) p.o. and i.p.; reduced intensity of inflammatory response when given i.p.                                                                                                                                                             | 2006 | Catelan et al. [321]                     |
| Adult female white New Zealand rabbits, anterior cruciate ligament transected, and medial meniscus removed; <i>Harpagophytum</i> extract (150 mg/day), standard food pellets as control; outcome suggests suppression of metalloproteinase-2 production.                                                                                     | 2006 | Chrubasik et al. [322], Chrubasik [289]  |
| Male ICR mice; formalin test; <i>Harpagophytum</i> extract (1.9% harpagoside, 30–300 mg/kg); significant dose-dependent attenuation of licking/biting and spinal nitrites/nitrates.                                                                                                                                                          | 2008 | Uchida et al. [323]                      |

Table 5. Cont.

| Study                                                                                                                                                                                                                                                                                                                                                                                                                                            | Year       | Reference                            |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|--------------------------------------|
| Rabbits after unilateral meniscectomy and transection of the anterior cruciate ligament; thickness, surface area, and volume of the tibial condylar cartilage per MRI; <i>H. procumbens</i> extract (14% harpagoside); difference in thickness and volume between healthy and operated leg slightly but not significantly smaller with <i>Harpagophytum</i> .                                                                                    | 2011, 2014 | Wachsmuth et al. [324], Wrubel [325] |
| BALB/c mice infected with <i>Salmonella enteritidis</i> ; leukocytes, neutrophils, and mononuclear cell counts, TNF- $\alpha$ , IL-4, 10, 12, histopathological analysis of the liver and small intestine; <i>H. procumbens</i> extract (150 $\mu$ g/day); downregulation of cell counts, TNF- $\alpha$ , IL-10 m 12, IL-4 increased, histopathology of liver unchanged, hypertrophy in the small intestine, reduced with <i>Harpagophytum</i> . | 2014       | Bisinotto [326]                      |
| Male SD rats; plantar incision and spared nerve injury; mechanical withdrawal threshold (MWT) test and ultrasonic vocalization (USVs); <i>H. procumbens</i> ethanolic extract (300 mg/kg, p.o.); MWT significantly increased, USVs reduced.                                                                                                                                                                                                      | 2014       | Lim et al. [327]                     |
| Rats; carrageenan-induced mechanical allodynia and thermal hyperalgesia, involvement of the hemeoxygenase (HO)-1/carbon monoxide (CO) pathway; <i>H. procumbens</i> extract (300 and 800 mg/kg i.p.); pretreatment with HO inhibitor reduced anti-hyperalgesic effect, pretreatment with hemin- or CO-releasing molecule induced antiallodynic response.                                                                                         | 2015       | Parenti et al. [328]                 |
| Rats; formalin-induced damage to cartilage tissue; combination of glucosamine hydrochloride, chondroitin sulfate, methylsulfonylmethane, <i>Harpagophytum</i> extract (3% harpagoside), and bromelain extract (500 mg/kg); malondialdehyde, NO, 8-hydroxyguanine, IL-1 $\beta$ , and TNF- $\alpha$ significantly lowered, glutathione significantly increased.                                                                                   | 2015       | Ucuncu et al. [329]                  |
| Rats, chronic constriction injury (CCI) of left sciatic nerve model; <i>Harpagophytum</i> extract + morphine, each at sub-analgesic dose; significant antiallodynic and anti-hyperalgesic effect suggesting synergistic effect.                                                                                                                                                                                                                  | 2016       | Parenti et al. [330]                 |
| Immunological angiogenesis induced by bronchoalveolar lavage (BAL) cells grafted into BALB/c mice skin; ethanolic extract of <i>Harpagophytum</i> , <i>Filipendula ulmaria</i> , and <i>Echinacea purpurea</i> ; significant reduction of newly formed blood vessels 1.2 and 0.6 mg daily.                                                                                                                                                       | 2016       | Radomska-Lesniewska et al. [331]     |

\* Species not specified; however, all specific attribution must be cautioned against due to the frequent admixture.

**Table 6.** Ex vivo experiments regarding analgesic/antinociceptive and anti-inflammatory effects of devil's claw preparations and compounds.

| Study                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Year       | Reference                       |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|---------------------------------|
| Human whole-blood anticoagulated with heparin; preincubated with <i>Harpagophytum</i> * extract or purified harpagoside; both dose-dependently inhibited cysteinyl-leukotriene and thromboxane B2 release after biotransformation.                                                                                                                                                                                                                                                             | 1996, 1997 | Tippler et al. [332,333]        |
| Human whole-blood assay (healthy and osteoarthritic) for COX-1 and COX-2 activity and NO production; <i>H. procumbens</i> extract and harpagoside; increased the activity of baseline COX-1 and COX-2 without LPS, crude extract did not alter COX activity; harpagoside inhibited COX-1, COX-2, and NO.                                                                                                                                                                                       | 2007       | Anauate [334]                   |
| Freshly excised porcine skin; dermal and transcutaneous delivery and effect on COX-2 expression in Western blotting and immunocytochemical assays; <i>Harpagophytum</i> extract in various vehicles, harpagoside, harpagide, 8-coumaroylharpagide, and verbascoside; ratio-dependent inhibition of COX-2 expression, higher penetration of all compounds from ethanol/water.                                                                                                                   | 2008       | Abdelouahab and Heard [335,336] |
| Freshly excised porcine skin; transcutaneous delivery and effect on COX-2, PGE2, 5-LOX, and inducible NO synthase (iNOS) expression in Western blotting and immunocytochemical assays; commercial <i>Harpagophytum</i> extracts, harpagoside, harpagide, 8-coumaroylharpagide, and verbascoside; ratio-dependent inhibition of COX-2 expression and PGE2, no significant effect on 5-LOX and iNOS, relative proportions of anti- and pro-inflammatory compounds in commercial products varied. | 2009, 2010 | Ouitas and Heard [337–339]      |



Table 6. Cont.

| Study                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Year | Reference           |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|---------------------|
| LPS-stimulated human whole-blood assay (healthy) for COX-1 and COX-2 activity and NO production, incubation of isolated fractions obtained by flash chromatography monitored with HPLC, TLC, and identified by <sup>1</sup> HNMR; fractions of <i>H. procumbens</i> extract; highest concentration of harpagoside inhibited COX-1, COX-2, and NO; iridoid pool increased COX-2 while NO and COX-1 activities remained unchanged, fraction containing cinnamic acid reduced NO only. | 2010 | Anaute et al. [340] |

\* Species not specified; however, all specific attribution must be cautioned against due to the frequent admixture.

**Table 7.** Mixed experiments regarding analgesic/antinociceptive and anti-inflammatory effects of devil's claw preparations and compounds.

| Study                                                                                                                                                                                                                                                                                                                                                                   | Type                 | Year | Reference                                        |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|------|--------------------------------------------------|
| Carrageenan-induced rat paw edema and adjuvant-induced arthritis in rats; arachidonic acid and prostaglandin synthetase incubated with various concentrations of indomethacin, acetylsalicylic acid, or <i>Harpagophytum</i> extract (not specified); no effect on edema, anti-inflammatory activity is not mediated by the inhibition of the prostaglandin synthetase. | In Vitro and in vivo | 1983 | Whitehouse et al. [341]                          |
| Cultured human mammary epithelial cells and female ICR mice; TPA-induced COX expression; <i>Harpagophytum</i> methanolic extract (10, 5, 1 µg/mL, 600, 300, 60 µg, respectively); inhibition of COX-2 expression in both models.                                                                                                                                        | In Vitro and in vivo | 2004 | Na et al. [342]                                  |
| Rat adjuvant-induced chronic arthritis model, LPS-stimulated mouse macrophage cells (RAW 264.7); <i>Harpagophytum</i> ethanolic extract; significant anti-inflammatory effect, and dose-dependent suppression of, IL-6 and TNF-α, respectively.                                                                                                                         | In Vitro and in vivo | 2010 | Inaba et al. [343]                               |
| Molecular docking study of harpagoside and harpagide with COX-2; binding energies were −9.13 and −5.53 kcal/mol respectively, finding both harpagoside and harpagide to be highly selective COX-2 inhibitors.                                                                                                                                                           | Simulation           | 2016 | Rahimi et al. [344]                              |
| Mouse myoblast C2C12, human colorectal adenocarcinoma HCT116 cell lines, isolated rat colon challenged with LPS; aqueous <i>Harpagophytum</i> extract (1–1000 µg/mL); HCT116 viability reduced, ROS production in both cell lines reduced, PGE <sub>2</sub> , 8-iso-PGF <sub>2α</sub> , serotonin, and TNF-α production inhibited.                                      | In Vitro and ex vivo | 2017 | Locatelli et al. [345],<br>Leporini et al. [346] |
| Antioxidant capacity, leukocyte ROS production, COX-2/PGE <sub>2</sub> pathway or cytokine secretions; <i>H. procumbens</i> methanolic extract; decreased the secretion of IL-21 and IL-23, increased TNF-α, IL-8, and IFN-γ, immune-stimulant effect.                                                                                                                  | In Vitro and ex vivo | 2019 | Cholet et al. [347]                              |
| LPS-stimulated wild-type (C57/BL6) male mice colon and HCT116 cells; experimental model of inflammatory bowel disease; <i>H. procumbens</i> aqueous extract; anti-inflammatory, antioxidative, and antimicrobial effects (against pathogen fungal strains), morphological alterations in the colon tissue indicated.                                                    | In Vitro and ex vivo | 2020 | Recinella et al. [348]                           |

\* Species not specified; however, all specific attribution must be cautioned against due to the frequent admixture.

Investigated targets for anti-inflammatory effects and their respective IC<sub>50</sub> (significant inhibitions, primary sources only) are summarized in Table 8.

**Table 8.** Anti-inflammatory targets of *Harpagophytum* preparations and compounds.

| Extract/Fraction                                                         | Harpagoside (%) | Cys-LT          | TXB <sub>2</sub> | Enzyme Inhibitors                | IC <sub>50</sub> |                 |                 | Reference |
|--------------------------------------------------------------------------|-----------------|-----------------|------------------|----------------------------------|------------------|-----------------|-----------------|-----------|
|                                                                          |                 |                 |                  |                                  | IL-6             | IL-1 $\beta$    | NF- $\kappa$ B  |           |
| Special extract WS1531                                                   | 7.3             | 9.2 $\mu$ M/L   | 55.3 $\mu$ M/L   |                                  |                  |                 |                 | [332,333] |
|                                                                          | 7.3             | 62 $\mu$ g/mL   | 373 $\mu$ g/mL   |                                  |                  |                 |                 | [285]     |
| Aqueous ethanolic <i>H. procumbens</i> extract                           | 2.1             | 1450 $\mu$ g/mL | -                |                                  |                  |                 |                 | [285]     |
|                                                                          |                 |                 |                  | 542 $\mu$ g/mL (HNE)             |                  |                 |                 | [199,201] |
|                                                                          |                 |                 |                  | 547.69/601.49 $\mu$ g/mL (MPO) * |                  |                 |                 | [349]     |
|                                                                          |                 |                 |                  |                                  | <100 $\mu$ g/mL  |                 |                 | [297]     |
| <i>H. procumbens</i> tincture                                            |                 |                 |                  | 915.55/776.49 $\mu$ g/mL (MPO) * |                  |                 |                 | [349]     |
| Aqueous ethanolic <i>H. zeyheri</i> extract                              |                 |                 |                  | 1012 $\mu$ g/mL (HNE)            |                  |                 |                 | [199,201] |
| Aqueous <i>H. procumbens</i> extract                                     | 8.9             |                 |                  |                                  |                  | 0.55 $\mu$ g/mL |                 | [350]     |
|                                                                          | 27              |                 |                  |                                  |                  | 0.2 $\mu$ g/mL  |                 | [350]     |
| Ethanolic <i>H. procumbens</i> extract                                   |                 |                 |                  | 65.5 $\mu$ g/mL (FAAH)           |                  |                 |                 | [304]     |
| Ethyl acetate fraction of aqueous ethanolic <i>H. procumbens</i> extract | 19.95           | 391 $\mu$ g/mL  | -                |                                  |                  |                 |                 | [285]     |
| Butanol fraction of aqueous ethanolic <i>H. procumbens</i> extract       | 19.5            | 565 $\mu$ g/mL  | 203 $\mu$ g/mL   |                                  |                  |                 |                 | [285]     |
| Methanolic <i>H. procumbens</i> extract                                  |                 |                 |                  |                                  |                  |                 | 1046 $\mu$ g/mL | [295]     |
| <i>H. procumbens</i> extracts and isolates                               |                 |                 |                  |                                  |                  |                 | ~125 $\mu$ g/mL | [296]     |
| <b>Isolated compounds</b>                                                |                 |                 |                  |                                  |                  |                 |                 |           |
| Harpagoside                                                              |                 | 30 $\mu$ M/L    | 48.6 $\mu$ M/L   |                                  |                  |                 |                 | [332,333] |
|                                                                          |                 | 39 $\mu$ M/L    | 49 $\mu$ M/L     |                                  |                  |                 |                 | [285]     |
|                                                                          |                 |                 |                  |                                  |                  |                 | 1041 $\mu$ g/mL | [295]     |
|                                                                          |                 |                 |                  | >600 $\mu$ g/mL (HNE)            |                  |                 |                 | [199,201] |
|                                                                          |                 |                 |                  | 92.7 $\mu$ M (AChE)              |                  |                 |                 | [351]     |
|                                                                          |                 |                 |                  | 95.6 $\mu$ M (AChE)              |                  |                 |                 | [351]     |
|                                                                          |                 |                 |                  |                                  |                  |                 | 96.4 $\mu$ M    | [293]     |
|                                                                          |                 |                 |                  |                                  | 14.04 $\mu$ M    |                 |                 | [302]     |
| Harpagide                                                                |                 |                 |                  |                                  |                  |                 | 1186 $\mu$ g/mL | [295]     |
| 8-PCHG                                                                   |                 |                 |                  | 179 $\mu$ g/mL (HNE)             |                  |                 |                 | [199,201] |
|                                                                          |                 |                 |                  | 95.6 $\mu$ M (AChE)              |                  |                 |                 | [351]     |
| Pagoside                                                                 |                 |                 |                  | 154 $\mu$ g/mL (HNE)             |                  |                 |                 | [199,201] |
| Caffeic acid                                                             |                 |                 |                  | 86 $\mu$ g/mL (HNE)              |                  |                 |                 | [199,201] |
| Acetoside                                                                |                 |                 |                  | >500 $\mu$ g/mL (HNE)            |                  |                 |                 | [199,201] |

Table 8. Cont.

|                        | IC <sub>50</sub>               | Reference |
|------------------------|--------------------------------|-----------|
|                        | 19.9 µM (AChE), 35 µM (BChE)   | [351]     |
| Isoacetocide           | 179 µg/mL (HNE)                | [199,201] |
|                        | 21.6 µM (AChE), 29.7 µM (BChE) | [351]     |
| Decaffeoylverbascoside | 16.1 µM (AChE), 46 µM (BChE)   | [351]     |
| 6'-O-Acetylacteosid    | 47 µg/mL (HNE)                 | [199,201] |

\* Formyl methionyl leucine phenylalanine- and arachidonic acid-stimulated, respectively.

Table 9 summarizes the results of pre-clinical experiments which studied other effects of *Harpagophytum* and its compounds.

Table 9. Experiments regarding other effects of devil's claw preparations and compounds.

| Effect      | Study                                                                                                                                                                                                                                                                                                                                                                                                            | Type     | Year       | Reference                           |
|-------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|------------|-------------------------------------|
| Antioxidant | Rats, <i>Harpagophytum</i> * extract, 100 and 200 mg/kg bw or selegiline i.p. for 1, 7, or 14 days; dose-dependent increase of superoxide dismutase, catalase, and glutathione peroxidase activities and reduction of lipid peroxidase similar to selegiline after 7 days.                                                                                                                                       | In Vivo  | 1998       | Bhattacharya and Bhattacharya [352] |
|             | Luminol-enhanced chemiluminescence in a xanthine/xanthine oxidase cell-free system; <i>Harpagophytum</i> root powder; superoxide and peroxy were scavenged dose-dependently.                                                                                                                                                                                                                                     | In Vitro | 2002       | Langmead et al. [353]               |
|             | Trolox equivalent antioxidant capacity (TEAC) assay; <i>Harpagophytum</i> aqueous extract (2.6% harpagoside) and harpagoside; extract rich in water-soluble antioxidants, harpagoside showed poor activity.                                                                                                                                                                                                      | In Vitro | 2003       | Betancor-Fernandez et al. [354]     |
|             | Rat renal mesangial cells; IL-1β-induced NO formation and transcriptional regulation of iNOS; <i>H. procumbens</i> extracts with varying harpagoside content and pure harpagoside; dose-dependent and harpagoside-independent inhibition of iNOS expression.                                                                                                                                                     | In Vitro | 2004       | Kaszkin et al. [350]                |
|             | <i>Harpagophytum</i> aqueous extract; protection from DNA-damaging effects of stannous chloride in proficient and deficient <i>E. coli</i> model; possible chelating, scavenger, or oxidant activity postulated.                                                                                                                                                                                                 | In Vitro | 2007       | Almeida et al. [355]                |
|             | Antioxidant characteristics using in vitro test systems, DPPH radical scavenging, stimulated nitrite generation, neutrophil superoxide anion generation, and neutrophil myeloperoxidase (MPO); <i>Harpagophytum</i> extract (1.2% harpagoside), tincture, harpagoside; dose-dependent effect in all models, minimal scavenging activity of harpagoside.                                                          | In Vitro | 2005, 2009 | Grant et al. [349], Grant [356]     |
|             | Antioxidant activities of total methanol extracts, fractions (phenylethanoids, terpenoids, and sugars), and β-OH-verbascoside, verbascoside, and leucosceptoside from cell suspension culture of <i>H. procumbens</i> ; DPPH, superoxide anion generation, and oxygen radical absorbance capacity (ORAC) assays; β-OH-verbascoside most active in DPPH and superoxide anion generation, leucosceptoside in ORAC. | In Vitro | 2010       | Georgiev et al. [357]               |
|             | Ferric-reducing antioxidant power test; <i>H. procumbens</i> crude methanolic extract, phenylethanoid-containing fraction, and verbascoside; strong ferrous ion-chelating capacity.                                                                                                                                                                                                                              | In Vitro | 2011       | Georgiev et al. [358]               |

Table 9. Cont.

| Effect             | Study                                                                                                                                                                                                                                                                                                                                                                                                      | Type                 | Year | Reference                                |
|--------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|------|------------------------------------------|
|                    | Brain homogenates, catalase activity and thiol levels, brain cortical slices; lipid peroxidation, antioxidant defenses, cell damage, respectively; <i>H. procumbens</i> infusion, crude extract, and fractions; dose-dependent inhibition of lipid peroxidation, ethyl acetate fraction had the highest antioxidant effects.                                                                               | In Vitro             | 2013 | Schaffer et al. [359,360]                |
|                    | Human neutrophils challenged with phorbol myristate acetate (PMA), opsonized <i>Staphylococcus aureus</i> , and <i>Fusobacterium nucleatum</i> ; 5 taxa of <i>Harpagophytum</i> , including one hybrid; high variability in suppression of respiratory burst, hybrid with highest antioxidant capacity but proinflammatory effect, three taxa with anti-inflammatory effect.                               | In Vitro             | 2016 | Muzila et al. [361]                      |
|                    | Adult male Wistar rats, fluphenazine-induced orofacial dyskinesia (OD); DPPH assay; ethyl acetate fraction of <i>H. procumbens</i> (10, 30, or 100 mg/kg i.p.); inhibition of vacuous chewing movements, decreased locomotion unchanged, protective against change in catalase activity, not against ROS increase.                                                                                         | In Vivo              | 2016 | Schaffer et al. [362]                    |
|                    | Porcine neutrophils; respiratory burst; harpagoside; significant inhibition of ROS production.                                                                                                                                                                                                                                                                                                             | In Vitro             | 2017 | Mosca et al. [363]                       |
|                    | Male Sprague–Dawley rats, modified rodent contusion model of spinal cord injury, murine BV-2 microglial cells; <i>H. procumbens</i> hydroethanolic extract (5.3% harpagoside, 300 mg/kg); behavioral and neurochemical parameters, improved, some significantly, in cell line, oxidative stress and inflammatory response were suppressed.                                                                 | In Vitro and in vivo | 2020 | Ungerer et al. [364]                     |
|                    | LPS-induced RAW 264.7 mouse and U937 human macrophages; DPPH and 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) assays; aqueous, ethanolic, and ethyl acetate extracts of <i>H. zeyheri</i> ; for all extracts, dose-dependent inhibition of IL-10 expression, ethyl acetate fraction with lowest IC <sub>50</sub> in both assays, NO and TNF- $\alpha$ inhibition similar to diclofenac. | In Vitro             | 2021 | Ncube et al. [365]                       |
| Antidiabetic       | Streptozotocin-induced diabetes mellitus in rats; <i>H. procumbens</i> root aqueous extract (50–800 mg/kg i.p.); significant reduction in blood glucose levels in normal and diabetic rats.                                                                                                                                                                                                                | In Vitro             | 2004 | Mahomed and Ojewole [317], Mahomed [318] |
| Anticholinesterase | Chick, guineapig, and rabbit isolated gastro-intestinal smooth muscle preparations; <i>H. procumbens</i> root aqueous extract (10–1000 $\mu$ g/mL); dose-dependent contractions of gastro-intestinal tract smooth muscles.                                                                                                                                                                                 | In Vitro             | 2005 | Mahomed [318], Mahomed et al. [366]      |
|                    | Spectrophotometric method using acetylthiocholine and butyrylcholine chloride as substrates; <i>H. procumbens</i> crude methanolic extract, phenylethanoid-containing fraction, and verbascoside; significant cholinesterase inhibitory activity.                                                                                                                                                          | In Vitro             | 2011 | Georgiev et al. [358]                    |
|                    | Spectrophotometric method, acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibition; <i>H. procumbens</i> ethyl acetate extract and fractions; inhibition by verbascosides > 60%                                                                                                                                                                                                            | In Vitro             | 2013 | Bae et al. [351]                         |
| Antimicrobial      | <i>Harpagophytum</i> extract (not specified) showed mild antifungal effects against <i>Penicillium digitatum</i> and <i>Botrytis cinerea</i> .                                                                                                                                                                                                                                                             | In Vitro             | 1985 | Guérin and Réveillère [367]              |
|                    | <i>Harpagophytum</i> dry extract (2.6% harpagoside) and harpagoside; inhibition of a panel (all) of aerobic bacteria, <i>C. krusei</i> , and two anaerobic bacteria strains, harpagoside without effect.                                                                                                                                                                                                   | In Vitro             | 2007 | Weckesser et al. [368]                   |

Table 9. Cont.

| Effect            | Study                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Type                 | Year       | Reference                       |
|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|------------|---------------------------------|
|                   | Chloroquine (CQ)-sensitive and CQ-resistant strains of <i>P. falciparum</i> , and cytotoxicity in CHO and HepG2 cells; extracts of <i>H. procumbens</i> aerial parts and seeds, and petrol ether of the root, (+)-8,11,13-totaratriene-12,13-diol and ferruginol, and CQ diphosphate as control; the two diterpenes showed significant inhibition of both strains without being cytotoxic.                                                                                                                                                                                                                                         | In Vitro             | 2003       | Clarkson et al. [200]           |
|                   | Female Balb/c mice, infected with <i>Toxocara canis</i> ; <i>Harpagophytum</i> ethanolic extract (100 mg/kg); decrease in eosinophil accumulation, IL-5 and IgE significantly decreased.                                                                                                                                                                                                                                                                                                                                                                                                                                           | In Vivo              | 2012, 2014 | Oliveira et al. [369–371]       |
|                   | <i>Harpagophytum</i> ethanolic extract showed dose-dependent effect on <i>Schistosoma mansoni</i> , mechanism of action proposed; proteins relevant for cellular homeostasis identified as possible targets.                                                                                                                                                                                                                                                                                                                                                                                                                       | In Vitro             | 2014       | Correia [372]                   |
|                   | Bacterial triggers of rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, and rheumatic fever; powdered <i>Harpagophytum</i> extracts, various solvents; inhibition of <i>Proteus mirabilis</i> , <i>Klebsiella pneumoniae</i> , <i>Acinetobacter baylyi</i> , <i>Pseudomonas aeruginosa</i> , and <i>Streptococcus pyogenes</i> throughout, methanolic extract more potent, no toxicity in <i>Artemia nauplii</i> bioassay. (Note: throughout the publication, the substance of investigation is mislabeled as devil's claw fruit, while it was, in fact, the root being investigated (pers. comm. Ian Cock, 2021)) | In Vitro             | 2017       | Cock and Bromley [373]          |
| Antimutagenic     | Cultured human lymphocytes; mutagenic activity of 1-nitropyrene (1-Npy) in cytokinesis-block micronucleus assay; <i>Harpagophytum</i> aqueous-ethanolic extract, harpagoside; genotoxicity significantly reduced for both, only harpagoside significantly reduced the mutagenicity of 1-Npy.                                                                                                                                                                                                                                                                                                                                       | In Vitro             | 2014, 2015 | Luigi [374], Luigi et al. [375] |
| Anti-osteoporotic | Male ICR mice, female C57BL/6J mice; receptor activator of nuclear factor $\kappa$ -B ligand (RANKL)-induced osteoclastogenesis; harpagoside; inhibition of RANKL, osteoclast formation, and LPS-induced bone loss, but not ovariectomy-mediated bone erosion.                                                                                                                                                                                                                                                                                                                                                                     | In Vitro             | 2015       | Kim et al. [376]                |
|                   | Mouse calvaria MC3T3-E1 cells; bone formation and resorption, bone-loss in ovariectomized (OVX) mouse model; harpagide; stimulated differentiation and maturation of osteoblast cells and suppressed RANKL-induced osteoclastogenesis, improved bone recovery in OVX model, inhibited markers of bone loss in the serum.                                                                                                                                                                                                                                                                                                           | In Vitro and in vivo | 2016       | Chung et al. [377]              |
|                   | Mouse calvaria MC3T3-E1 cells; bone formation and resorption, bone-loss in ovariectomized (OVX) mouse model; harpagoside; stimulated differentiation and maturation of osteoblast cells and suppressed RANKL-induced osteoclastogenesis, improved bone recovery in OVX model, inhibited markers of bone loss in the serum.                                                                                                                                                                                                                                                                                                         | In Vitro and in vivo | 2017       | Chung et al. [378]              |
| Cardiovascular    | Frog and guineapig hearts, cats; cardiac muscle contraction and blood pressure, dose-dependent positive and negative inotropic effects, no effect on blood pressure.                                                                                                                                                                                                                                                                                                                                                                                                                                                               | In Vitro and in vivo | 1965       | Vollmann [379]                  |
|                   | Normotensive rats, rabbit heart; methanolic extract of <i>Harpagophytum</i> , harpagoside, harpagide; decrease in blood pressure and heart rate observed, less with harpagoside; extract mild inotropic at lower and negative inotropic at higher doses, harpagoside more negative chronotropic and positive inotropic, harpagide only slightly negative chronotropic but considerably negative inotropic.                                                                                                                                                                                                                         | In Vitro and in vivo | 1984       | Circosta et al. [380]           |



Table 9. Cont.

| Effect                            | Study                                                                                                                                                                                                                                                                                                                                   | Type                 | Year | Reference                                |
|-----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|------|------------------------------------------|
|                                   | Rat heart; methanolic extract of <i>Harpagophytum</i> (8.5% harpagoside and 10.5% total iridoids) and harpagoside; significant, dose-dependent, protective action toward hyperkinetic ventricular arrhythmias.                                                                                                                          | In Vitro             | 1985 | De Pasquale et al. [381]                 |
|                                   | Langendorff preparations of rat heart; ischemic perfusion induced hyperkinetic ventricular arrhythmia; <i>H. procumbens</i> , harpagoside; significant, dose-dependent protective action for both.                                                                                                                                      | In Vitro             | 1985 | De Pasquale et al. [382]                 |
|                                   | Guineapig ileum and rabbit jejunum; <i>Harpagophytum</i> extract, harpagoside, harpagide; spasmolytic effect, strongest for harpagoside.                                                                                                                                                                                                | In Vitro             | 1985 | Occhiuto et al. [383]                    |
|                                   | Dogs; harpagoside, harpagide (3.4 mg/kg); decrease of mean aortic pressure with harpagoside.                                                                                                                                                                                                                                            | In Vivo              | 1990 | Occhiuto and de Pasquale [384]           |
|                                   | Multiple mammalian animal models; <i>H. procumbens</i> root aqueous extract (10–400 mg/kg i.v., 10–1000 µg/mL); dose-dependent, significant hypotensive, cardio-depressant, and vasorelaxant effects.                                                                                                                                   | In Vitro and in vivo | 2004 | Mahomed and Ojewole [385], Mahomed [318] |
| Neuroprotective                   | Pentylentetrazole (PTZ)-, picrotoxin (PCT)-, and bicuculline (BCL)-induced seizures in mice; <i>H. procumbens</i> aqueous extract (100–800 mg/kg i.p.); PZT-induced seizures significantly reduced, PCT and BCL to a lesser extent, CNS depressed.                                                                                      | In Vivo              | 2006 | Mahomed and Ojewole [386]                |
|                                   | Rat hypothalamic (Hypo-E22) cells and rat cortex challenged with amyloid $\beta$ -peptide; <i>H. procumbens</i> aqueous extract; increased brain-derived neurotrophic factor gene expression and decreased TNF- $\alpha$ gene expression in Hypo-E22 cells, alleviated decreased monoaminergic signaling in cortex presynaptic endings. | In Vitro and ex vivo | 2017 | Ferrante et al. [387]                    |
|                                   | Male Wistar rats; chronic cerebral hypoperfusion model; harpagoside (15 mg/kg, 60 days); symptoms of vascular dementia spatial and fear memory impairments restored, phosphatase and tensin homolog (PTEN) significantly suppressed.                                                                                                    | In Vivo              | 2018 | Chen et al. [388]                        |
|                                   | Female Wistar albino rats, arsenic induced neurotoxicity; <i>Harpagophytum</i> powder (200 and 400 mg/kg, p.o.); behavioral and biochemical parameters improved significantly.                                                                                                                                                          | In Vivo              | 2020 | Peruru et al. [389]                      |
| Immunomodulatory/<br>thymomimetic | Maturation of mice thymocytes in the presence of a glucocorticosteroid, cytotoxicity by microscopy and flow cytometry; ethanolic extract of <i>Harpagophytum</i> , <i>Filipendula ulmaria</i> , and <i>Echinacea purpurea</i> , various dilutions; 17% increase in the number of surviving cells.                                       | In Vitro             | 2002 | Prosinska et al. [390]                   |
| Anorexigenic                      | Male C57BL/6 mice, calcium mobilization and growth hormone secretagogue receptor (GHS-R1a) internalization; <i>Harpagophytum</i> root powder; significantly increased cellular calcium influx but no induction of GHS-R1a receptor internalization, significant anorexigenic effect.                                                    | In Vivo              | 2014 | Torres-Fuentes et al. [391]              |
|                                   | Male Wistar rats; obestatin secretion; <i>Harpagophytum</i> hydroalcoholic extract (150, 300, and 600 mg/kg); significantly increased serum levels of obestatin and reduced body weight at 300 and 600 mg/kg.                                                                                                                           | In Vivo              | 2016 | Saleh et al. [392]                       |
| Metal accumulation                | Rats, supplemented with lead acetate; <i>Harpagophytum</i> infusion (30 mg/kg); significant reduction of lead deposits                                                                                                                                                                                                                  | In Vitro             | 1975 | Int. Bio Research [393]                  |

\* Species not specified; however, all specific attribution must be cautioned against due to the frequent admixture.

Primary—anti-inflammatory, analgesic/antinociceptive, and antioxidant—effects have been demonstrated in multiple in vitro, in vivo, and ex vivo assays with crude extracts, fractions, and isolated compounds of *Harpagophytum*. However, experiments show some inconsistencies, likely caused by deviations in experimental models and insufficient characterization of the purportedly active compounds, as well as variation in solvent systems [394–396]. Further, the consolidated data show that efficacy cannot be clearly attributed to any one of the compounds present in *Harpagophytum*. Focus on harpagoside—albeit serving as a convenient marker—cannot be substantiated in an efficacy context. On the other hand, the presence and effect of verbascoside in *Harpagophytum*, a compound with well-documented anti-inflammatory properties, has not been adequately studied.

### 11.2. Pharmacokinetics

Most of the available pharmacokinetics data were created as a byproduct or in the context of pharmacological experiments with *Harpagophytum* preparations or its compounds. Vanhaelen [52] experimented with harpagoside and harpagide under conditions mimicking those found in the stomach and concluded by suggesting enteric-coated preparations for harpagoside to slow down acid hydrolysis. Chrubasik [217] investigated release and stability of harpagoside in gastric and intestinal fluids and stability for 3 and 6 h, respectively. The author also found harpagoside to be of low bioavailability, a daily dose of 100 mg could not be detected in serum or urine. Chrubasik et al. (2000) [238] established an octanol–water distribution coefficient of approximately 4 that is not dependent on pH or temperature.

Neither *Harpagophytum* ethanolic extract nor harpagoside had a relevant effect on cytochrome P (CYP) 450 3A4 in vitro [397]. An investigation of different *Harpagophytum* extracts elucidated maximum levels of plasma harpagoside after 1.3 to 2.5 h and suggested a correlation between serum harpagoside levels and inhibition of leukotriene biosynthesis in vitro and ex vivo [285,398]. In human liver microsomes and subtype-specific CYP substrates, *Harpagophytum* at a dose derived from [157] activated CYP 2E1 and inhibited CYP 2C19 [399]. Inhibition of CYP 450 was shown for methanolic extracts of *H. procumbens*, and while inhibition of CYP 1A2 and 2D6 was relatively low, moderate inhibition of CYP 2C8/9/19 and 3A4 was noted ( $IC_{50}$  between 100 and 350  $\mu\text{g/mL}$ ) [400]. However, the impact on drugs metabolized via those enzymes is merely theoretical. Romiti et al. [401] found *Harpagophytum* to interact with the multidrug transporter ABCB1/P-glycoprotein, unrelated to relative harpagoside content. Modarai et al. [402] found *Harpagophytum* preparations, but not harpagoside or harpagide, to weakly inhibit CYP 3A4, but deemed clinical relevance unlikely.

### 11.3. Toxicology

Acute and chronic toxicity have been investigated for the herbal substance, its preparations, and compounds isolated from *Harpagophytum*. Multiple publications cite an unpublished experiment by Albus (1958) in which an  $LD_{50}$  in mice was established for a liquid extract (not specified) at 34 mL/kg i.v. and 220 mL/kg p.o. [22,42,51,120]. An  $LD_{50}$  in rats was given at 10 g/kg for a spray extract and in mice at 1 g/kg for harpagoside [403]. Vollmann [379] established an  $LD_{50}$  of 23 and 10 mL/kg for an infusion and a chloroform/butanolic extract (4:1), respectively. Möse [404], in an unpublished report (cited in [27,44,67,405]) conducted toxicity tests with a *Harpagophytum* infusion in primate and chicken tissue cultures, and no effect on cell development was found, nor did the infusion promote growth of Ehrlich ascites carcinoma in mice. Eichler and Koch referenced toxicity at above 0.5 g/kg without citation [305]. Erdös and colleagues [308] demonstrated *Harpagophytum* aqueous, methanolic, and butanolic extracts to be effectively non-toxic ( $LD_0$  at 4640 mg/kg p.o. and >1000 mg/kg i.v.), and for harpagoside, a  $LD_0$  of 395 mg/kg and a  $LD_{50}$  of 511 mg/kg. Marzin (1978, cited in [67]) confirmed these results. The same author investigated the toxicity of an extract (2.7% total iridoids), p.o. or i.p., in rats and mice. Administration p.o. was effectively non-toxic, while i.p., some toxicity was observed with

a calculated LD<sub>50</sub> of 10 g/kg (Marzin, 1981, cited in [274]). Vanhalen and colleagues tested toxicity of harpagoside and harpagide in mice and established an LD<sub>50</sub> of 1 and 3.2 g/kg, respectively [224]. Schmidt [44] elaborated unpublished toxicological investigations with *Harpagophytum* D2 and Harpagosan (DER 2:1) [406,407], establishing an LD<sub>50</sub> of 20 mL/kg and >30 mg/kg, respectively. Whitehouse et al. [341] established an LD<sub>50</sub> at 13.5 g/kg p.o. for a *Harpagophytum* root extract (not specified) in mice and no toxicity at 7.5 g/kg over three weeks in rats, while 2 g/kg over one week showed no impact on liver parameters. Ibrahim et al. [408] conducted a battery of toxicity studies in mice (acute, sub-acute, and chronic) with a commercial product (Boiron, France—composition not declared) and found no clinically relevant changes in any of the tested outcomes, attributing a slight increase in liver enzymes to the anti-inflammatory effect. Al-Harbi and colleagues [409] found no oral acute toxicity in mice at 1 and 3 g/kg *Harpagophytum* powder. In a 90-day chronic toxicity study (test substance not characterized), no clinically relevant changes in tested parameters were established, except for a significant decrease in blood sugar and uric acid levels. Both chronic assessments, however, must be considered inadequate due to the insufficiently characterized test material. Allard et al. [410] discussed herb-induced nephrotoxicity, and in that context, called for further investigation of whether a theoretical impact of *Harpagophytum* on major renal transport processes is of clinical relevance. Joshi et al. [411] investigated the toxicology of a *H. procumbens* aqueous-ethanolic extract (1 g/kg/day, equivalent to 7.5–10× the human recommended dose) in male and female Sprague Dawley rats over 4 and 12 weeks. While no significant histopathological effects were found, the study yielded significant—albeit not clinically relevant—sex-related differences in blood chemistry. All these results stand in stark contrast to those of Zorn [116], casting considerable doubt over the authenticity of the plant material used in his experiments.

Mahomed and Ojewole [412,413] conducted experiments in vitro suggesting spasmogenic and uterotonic actions for an *H. procumbens* aqueous extract (10–1000 µg/mL). Whether these results are of clinical relevance in vivo remains to be established (see Section 11.2). Pearson [414] studied the reproductive toxicity of a combination product containing *Harpagophytum* (exact composition not disclosed) for veterinary use in pregnant female Sprague Dawley rats and showed no signs of toxicity. The study, however, is poorly reported and of limited relevance given the unknown composition of the test substance. Contrarily, Davari and colleagues [415] reported teratogenic effects and histopathological changes in fetal tissues (but no significant structural malformations or abnormalities) from an experiment with *H. procumbens* (200, 400, 600 mg/kg) in pregnant Balb/C mice.

## 12. Clinical Research

### 12.1. Efficacy

The efficacy of devil's claw has been investigated in more than 50 human studies, and case reports and observational studies are summarized in Table 10, while randomized, controlled trials (RCTs) are summarized in Table 11. Indications were primarily degenerative joint diseases as well as low back pain. Trials utilized a variety of methodological designs, with different preparations of devil's claw and daily doses of harpagoside, varying from <30 to >100 mg. While harpagoside is considered to contribute to the overall activity of devil's claw preparations, it is not yet fully understood which other compounds may also be of relevance. Furthermore, an investigation into the harpagoside content of commercially available devil's claw preparations revealed substantial variation, with contents often below the recommended daily dose of 4.5–9 g crude drug (equivalent >50 mg harpagoside) [173,232–234,237,416].

Trials have been reviewed systematically with regards to their quality and results concerning safety and efficacy of *Harpagophytum* preparations in publications between 1973 and 2019 [17,23,139,156,417–433]. Another set of reviews considered the efficacy of devil's claw preparations or its active compounds in specific need states [23,130,434–488]. All trials observed improvement of the outcome criteria under treatment (some significant), however, significant superiority of the *Harpagophytum* preparations vs. conventional NSAIDs was

not reported. This is partly because most trials were observational and/or comparative, while the outcomes of placebo-controlled trials were often inconclusive or overshadowed by methodological deficiencies. Many trials allowed for conventional emergency or co-medication, which further limits the value of the data collected. Despite some studies providing evidence for the effectiveness of certain preparations, the overall quality of evidence is not sufficient. Furthermore, the relevance of early studies with homeopathic dilutions—while included here for completeness’ sake—is limited from a perspective of rational phytotherapy.

**Table 10.** Case reports and observational studies conducted between 1971 and 2021.

| Indication                   | Trial Type, Size | Results                                                                                                                                                                                                                                                                          | Year | Reference                     |
|------------------------------|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|-------------------------------|
| Chemosis                     | CR<br>1          | Initial treatment with multiple preparations that did not lead to improvement, then with 300 mg <i>Harpagophytum</i> extract (not specified) 3 times daily, orally, for 6 months, leading to drastic improvement.                                                                | 1983 | Belaiche [489]                |
| Familial Mediterranean fever | CR<br>17         | <i>Harpagophytum</i> extracts characterized as aqueous (DER 1:2.4, 2.5% harpagoside)—this characterization may also apply to previous trials by Belaiche and Dahout (see above)—6–9 g single dose, duration not provided; significantly decreased recurrence in 80% of patients. | 1983 | Belaiche [490]                |
| Cancer                       | CR<br>2          | Tumor regression after taking <i>Harpagophytum</i> extract (500 mg daily) and/or Essiac respectively, without cytotoxic therapy.                                                                                                                                                 | 2009 | Wilson [491]                  |
| DJD                          | O<br>~120        | <i>Harpagophytum</i> D4–D6, IA, and D1 orally; 1–6 months; substantial improvement of symptoms in most cases.                                                                                                                                                                    | 1971 | Beham [492]                   |
| CP                           | O<br>60          | <i>Harpagophytum</i> D2, IA, plus tea (2–3 tsp per 1 L water) or 3 × 2 tablets orally, duration not provided; dose-dependent response; 60% substantial improvement of symptoms, 20% improvement, 20% no change.                                                                  | 1972 | Schmidt [43]                  |
| CP, DJD                      | O<br>146         | <i>Harpagophytum</i> D2, IA, duration not provided; improvement in 134 patients.                                                                                                                                                                                                 | 1972 | Zimmermann, cited in [130]    |
| DJD                          | O<br>25          | <i>Harpagophytum</i> D2–D3, IA, and SC, 1–2 mL, pain-free after 6 injections, or tea (1 tsp per 300 mL) daily for 3–6 weeks.                                                                                                                                                     | 1972 | Brantner [493]                |
| DJD                          | O<br>70          | <i>Harpagophytum</i> D2, IA, some + tea, some + indometacin, duration not provided; improvement in 90% of patients.                                                                                                                                                              | 1976 | Wilhelmer, cited in [44]      |
| CP, DJD                      | O<br>21+         | <i>Harpagophytum</i> D1–D3, IA, SC, and i.v., tea, orally, duration not provided; significant improvement in 30% of patients.                                                                                                                                                    | 1977 | Zimmermann [494]              |
| DJD                          | O<br>84          | 250 or 500 mg <i>Harpagophytum</i> extract (not specified) 3 times daily orally for 2–6 months, improvement in 72% of patients.                                                                                                                                                  | 1979 | Dahout, cited in [495]        |
| CP, DJD                      | O<br>600         | Harpagosan tea (2 tea bags in 500 mL water daily) plus D2 SC for up to 6 months. Symptoms disappeared in 200 patients; 400 patients improved after having received additional conventional medication for the first 3–4 weeks.                                                   | 1983 | Warning cited in Schmidt [44] |
| Rheumatoid arthritis         | O<br>1           | Improvement after treatment with low-potency <i>Harpagophytum</i> i.v. and orally, duration not provided.                                                                                                                                                                        | 1987 | Stübler [496,497]             |
| DJD                          | O<br>553         | Patients treated with 2–6 capsules of 400 mg <i>Harpagophytum</i> extract (1.5–2.5:1) for 8 to 180 days. Outcomes confirmed RCT results in terms of efficacy and safety.                                                                                                         | 2000 | Müller et al. [498]           |
| DJD                          | O<br>255         | Post-marketing surveillance study of biopsychosocial determinants and treatment response. Patients treated with <i>Harpagophytum</i> extract (60 mg harpagoside/day) for 2 months. Outcome parameters were significantly worse in non-responders.                                | 2009 | Thanner et al. [499]          |

Table 10. Cont.

| Indication                                             | Trial Type, Size                   | Results                                                                                                                                                                                                                                               | Year | Reference                  |
|--------------------------------------------------------|------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|----------------------------|
| CP, DJD, dyspepsia, hypercholesterolemia, detoxication | O, CR<br>700+                      | <i>Harpagophytum</i> tea, up to 12 weeks, D2, SC, 20 injections, further improvement with additional D2 i.v. and tea.                                                                                                                                 | 1978 | Schmidt [130]              |
| Diabetes mellitus with lipometabolic disorder          | OT<br>10                           | 4 patients 3 weeks, 6 patients 4 and 3 weeks, over a total of 6 months; <i>Harpagophytum</i> tea, amount not specified; cholesterol, lipid, and blood sugar levels normalized.                                                                        | 1974 | Hoppe [500]                |
| Hypercholesterolemia and hyperuricemia                 | OT<br>100                          | <i>Harpagophytum</i> tea, 2 tea bags per $\frac{1}{2}$ L water, 3× daily before meals 1/3 of the tea; 20–21 days; lowered cholesterol levels in 80%, normal levels in 45%, 66% improvement in hyperuricemia.                                          | 1978 | Grünewald [405]            |
| DJD                                                    | OT<br>13                           | <i>Harpagophytum</i> extract (<30 mg harpagoside/day), for 6 weeks, followed up for another six weeks; no overall statistically significant improvements in the conditions.                                                                           | 1981 | Grahame and Robinson [501] |
| DJD                                                    | OT<br>630                          | 42% to 85% of the patients (depending on grouping) showed improvements after 6 months with <i>Harpagophytum</i> extract (>90 mg harpagoside/day).                                                                                                     | 1982 | Belaiche [502]             |
| DJD                                                    | OT<br>38                           | Comparison of <i>Formica rufa</i> D6 with <i>Harpagophytum</i> D4, for 3 months; improvement in pain severity and mobility with both, <i>Formica rufa</i> slightly superior.                                                                          | 1991 | Kröner [503]               |
| Effect on eicosanoid biosynthesis                      | OT<br>34 (25/8) healthy volunteers | <i>Harpagophytum</i> , 4 capsules (500 mg powder, 3% of total glucosiridoids) daily for 21 days. No effect vs. control.                                                                                                                               | 1992 | Moussard et al. [504]      |
| MSD                                                    | OT<br>102 (51,51)                  | Patients treated with <i>Harpagophytum</i> extract (30 mg harpagoside/day) or conventional therapy (mainly oral NSAIDs). Number of pain-free patients and changes in Arhus scores after 4 and 6 weeks of treatment was comparable between the groups. | 1997 | Chrubasik et al. [505]     |
| DJD                                                    | OT<br>43                           | <i>Harpagophytum</i> powder 3 g daily for 60 days. Reduction of pain intensity in 89%, increased mobility in 83%.                                                                                                                                     | 1997 | Pinget and Lecomte [506]   |
| MSD                                                    | OT<br>2053                         | Patients treated with <i>Harpagophytum</i> extract (30 mg harpagoside/day) for 6 weeks. Symptoms improved over time.                                                                                                                                  | 1999 | Schwarz et al. [507]       |
| DJD                                                    | OT<br>45                           | Patients treated with <i>Harpagophytum</i> extract (30 mg harpagoside/day) for two weeks plus NSAID treatment, and devil's claw alone, for four weeks. No worsening of scores was observed during treatment with devil's claw alone.                  | 2000 | Szczepanski et al. [508]   |
| MSD                                                    | OT<br>1026                         | Patients treated with <i>Harpagophytum</i> extract (30 mg harpagoside/day) for 6 weeks. Symptoms improved.                                                                                                                                            | 2000 | Usbeck [509,510]           |
| MSD                                                    | OT<br>130                          | Patients treated with <i>Harpagophytum</i> extract (~30 mg harpagoside/day) for 8 weeks. Arhus back pain index decreased significantly during treatment. Other measures also improved significantly.                                                  | 2001 | Laudahn et al. [511–513]   |
| DJD                                                    | OT<br>583                          | Patients treated with <i>Harpagophytum</i> extract (~30 mg harpagoside/day) for 8 weeks. Symptoms improved and the dose of co-medication (NSAIDs) could be reduced.                                                                                   | 2001 | Schendel [514]             |
| DJD                                                    | OT<br>675                          | Patients treated with <i>Harpagophytum</i> extract (~30 mg harpagoside/day) for 8 weeks. Efficacy rated good or very good in 82% of cases. The symptom scores decreased, and co-medication was successfully reduced or even discontinued.             | 2001 | Ribbat and Schakau [515]   |



Table 10. Cont.

| Indication    | Trial Type, Size        | Results                                                                                                                                                                                                                                                                                                                                                                                            | Year       | Reference                         |
|---------------|-------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|-----------------------------------|
| MSD           | OT<br>250               | Patients treated with <i>Harpagophytum</i> extract (60 mg harpagoside/day) for 8 weeks. Both generic and disease-specific outcome measures improved.                                                                                                                                                                                                                                               | 2002       | Chrubasik et al. [516]            |
| DJD           | OT<br>614               | Patients treated with <i>Harpagophytum</i> extract (480 mg twice daily) for 8 weeks. Symptoms improved in the majority of patients; treatment was well-tolerated.                                                                                                                                                                                                                                  | 2003       | Kloker and Flammersfeld [517,518] |
| DJD           | OT<br>75                | Patients treated with <i>Harpagophytum</i> extract (50 mg harpagoside/day) for 12 weeks. WOMAC index and 10 cm VAS pain scale improved notably.                                                                                                                                                                                                                                                    | 2003       | Wegener and Lüpke [519,520]       |
| MSD           | OT<br>99                | Patients treated with <i>Harpagophytum</i> extract (~30 mg harpagoside/day) for 6 weeks. Symptoms improved.                                                                                                                                                                                                                                                                                        | 2005       | Rütten and Kuhn [521]             |
| MSD           | OT<br>102<br>(29/22/51) | Patients treated with <i>Harpagophytum</i> extract (~30 mg harpagoside/day) and/or conventional therapy for 6 weeks. Efficacy was found in all groups, advantages for devil's claw were not statistically significant.                                                                                                                                                                             | 2005       | Schmidt et al. [522,523]          |
| DJD           | OT<br>65                | Patients treated with combination of <i>Harpagophytum procumbens</i> , <i>Zingiber officinale</i> , and <i>Urtica</i> sp. (ratio not disclosed) for 8 weeks. Improvements in all efficacy parameters were observed.                                                                                                                                                                                | 2005       | Sohail et al. [524]               |
| Endometriosis | OT<br>6, 12             | Patients treated with <i>Harpagophytum</i> extract (1600 mg daily) for 12 weeks. Reduction of symptoms in 4 (6) patients after 4 weeks, in all patients after 12 weeks.                                                                                                                                                                                                                            | 2005, 2006 | Arndt et al. [525,526]            |
| DJD           | OT<br>259               | Patients treated with <i>Harpagophytum</i> extract (1.5–3:1, 960 mg daily) and NSAIDs for 8 weeks. At the end of the treatment, 44.8% could decrease NSAID dosage. All parameters improved significantly.                                                                                                                                                                                          | 2006       | Suter et al. [527,528]            |
| MSD           | OT<br>114               | Patients treated with <i>Harpagophytum</i> extract (60 mg harpagoside/day) for up to 54 weeks. Most outcome scores improved significantly over time.                                                                                                                                                                                                                                               | 2007       | Chrubasik et al. [529]            |
| DJD           | OT<br>42                | Patients treated with combination of <i>Harpagophytum</i> (1800 mg), <i>Curcuma longa</i> (1200 mg), and bromelain (900 mg) daily, plus conventional therapies for 2 weeks. Clinically relevant improvement of joint pain scores in all patients.                                                                                                                                                  | 2014       | Conrozier et al. [530]            |
| DJD           | OT<br>20                | Patients treated with combination of 500 mg glucosamine sulfate, 400 mg chondroitin sulfate, 10 mg collagen type II, and 40 mg <i>Harpagophytum</i> per day for 12 months. Femoral hyaline cartilage thickness significantly improved and radiographic progression of knee osteoarthritis delayed.                                                                                                 | 2019       | Vreju et al. [531]                |
| MSD           | OT<br>39/40/16          | Otherwise healthy subjects with mild/moderate neck/shoulder pain related to sport; cream containing a combination of ingredients, including <i>H. procumbens</i> root extract + standard treatment, standard treatment, diclofenac patch + standard treatment respectively, for 2 weeks; significant improvement in pain, stiffness, mobility, and working capacity, compared to non-cream groups. | 2021       | Hu et al. [532]                   |

CP = chronic polyarthritis; IA = intra-articular; SC = subcutaneous; DJD = degenerative joint diseases (osteoarthritis); MSD = musculo-skeletal disorders (low back pain); OT = observational trial; O = observation; CR = case report; NSAID = non-steroidal anti-inflammatory drug; WOMAC = Western Ontario and McMaster Universities.

Table 11. RCTs conducted between 1980 and 2017.

|     |                       |                                                                                                                                                                                                                                                                                                                             |       |                                    |
|-----|-----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|------------------------------------|
| DJD | RCT<br>39             | 400 mg <i>Harpagophytum</i> extract (not specified), and 25 mg diclofenac, or placebo 3× daily for 6 months. Overall confirmation of anti-inflammatory effects without side effects.                                                                                                                                        | ~1980 | Chaouat, cited in [66,67]          |
| DJD | RCT<br>50 (25/25)     | <i>Harpagophytum</i> extract (<30 mg harpagoside/day) and phenylbutazone (300 mg per day for the first four days, then 200 mg) respectively, for 28 days. Devil's claw found equally effective to phenylbutazone.                                                                                                           | 1980  | Schrüffler [533]                   |
| DJD | RCT<br>50 (25/25)     | Patients treated with <i>Harpagophytum</i> extract (<20 mg harpagoside/day) or placebo for three weeks showed a significant decrease in pain severity vs. placebo.                                                                                                                                                          | 1984  | Guyader [534]                      |
| DJD | RCT<br>100 (50/50)    | Patients treated with <i>Harpagophytum</i> extract (60 mg harpagoside/day) or placebo for 30 days. Only 6 patients in the verum group still experienced moderate pain vs. 32 in the placebo group.                                                                                                                          | 1990  | Pinget and Lecomte [535]           |
| DJD | RCT<br>89 (45/44)     | Patients treated with <i>Harpagophytum</i> extract (60 mg harpagoside/day) or placebo for two months. Significant decrease in severity of pain and significant increase in spinal and cofexomoral mobility vs. placebo.                                                                                                     | 1992  | Lecomte and Costa [536]            |
| MSD | RCT<br>118 (59/59)    | Patients treated with <i>Harpagophytum</i> extract (50 mg harpagoside/day) or placebo for 4 weeks. Treatment group used less analgesics, had greater improvement in median Arhus scores (20% vs. 8%; $p < 0.059$ ), and had more patients pain-free at the end (9/51 vs. 1/54; $p = 0.008$ ).                               | 1996  | Chrubasik et al. [537–539]         |
| MSD | RCT<br>109 (54/55)    | Patients treated with <i>Harpagophytum</i> extract (50 mg harpagoside/day) or placebo for 4 weeks. Rescue medication: tramadol. Significant improvement in Arhus index and pain index, and co-medication reduced vs. placebo.                                                                                               | 1997  | Chrubasik et al. [540]             |
| DJD | RCT<br>100 (50/50)    | Patients treated with <i>Harpagophytum</i> extract (30 mg harpagoside/day) or placebo for 30 days. Favorable effects were evident after 10 days vs. placebo.                                                                                                                                                                | 1997  | Schmelz and Hämmerle [541]         |
| MSD | RCT<br>197 (65/66/66) | Patients treated with <i>Harpagophytum</i> extract (50 mg (1), 100 mg (2) harpagoside/day) or placebo (3) for four weeks. 6, 10, and 3 patients were pain-free in groups 1, 2 and 3, respectively. Arhus index score decreased but not statistically significant. Dose-related effect not confirmed.                        | 1999  | Chrubasik et al. [542]             |
| DJD | RCT<br>122 (62/60)    | Patients treated with <i>Harpagophytum</i> extract (57 mg harpagoside/day) or diacerhein at 100 mg daily for four months. Results showed significant improvement in both groups at a similar rate.                                                                                                                          | 2000  | Chantre et al. [543,544]           |
| MSD | RCT<br>63 (31/32)     | Patients treated with <i>Harpagophytum</i> extract (~30 mg harpagoside/day) or placebo for 4 weeks. Significant efficacy for visual analogue scale, pressure algometer test, muscle stiffness test, and muscular ischemia test. No differences to placebo in anti-nociceptive muscular reflexes or electromyogram activity. | 2000  | Göbel et al. [512,513,545,546]     |
| DJD | RCT<br>46 (24/22)     | Patients treated with ibuprofen (800 mg) and <i>Harpagophytum</i> extract (~30 mg harpagoside/day) or placebo for 20 weeks. WOMAC scores decreased similarly, but during an ibuprofen-free period, symptoms worsened less than 20% for 71% of devil's claw patients vs. 41% of placebo patients.                            | 2001  | Frerick et al. [547]               |
| DJD | RCT<br>78 (39/39)     | Patients treated with <i>Harpagophytum</i> extract (~30 mg harpagoside/day) or placebo for 20 weeks. Co-medication ibuprofen. Symptoms improved similarly for both groups.                                                                                                                                                  | 2002  | Biller [548]                       |
| MSD | RCT<br>88 (44/44)     | Patients treated with <i>Harpagophytum</i> extract (60 mg harpagoside/day) for 6 weeks or 12.5 mg/day of rofecoxib. Outcome scores improved similarly for both groups. Follow-up confirmed the results of the pilot study.                                                                                                  | 2003  | Chrubasik et al. [538,539,549–552] |

Table 11. Cont.

|                                       |                      |                                                                                                                                                                                                                                                                                                                                   |      |                          |
|---------------------------------------|----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|--------------------------|
| MSD                                   | RCT<br>97 (36/31/30) | Patients treated with <i>Harpagophytum</i> extract (~30 mg harpagoside/day) or NSAID (Voltaren 150 mg or Vioxx 12.5 mg), duration not provided; outcomes show equality of treatment.                                                                                                                                              | 2005 | Lienert et al. [553,554] |
| DJD                                   | RCT<br>60 (30/30)    | Patients treated with combination of <i>Harpagophytum</i> and <i>Apium graveolens</i> extract (cream, 1.5 cm, twice daily) or placebo for 2 weeks. Treatment group showed significant improvement in algometer, flexion, and extension readings.                                                                                  | 2006 | Pillay [555]             |
| Sore throat after tracheal intubation | RCT<br>60 (30/30)    | Patients treated with <i>Harpagophytum</i> extract (480 mg one hour before intubation) or placebo plus premedication (fentanyl, midazolam, propofol). No significant difference was observed between groups.                                                                                                                      | 2016 | Anvari et al. [556]      |
| DJD                                   | RCT<br>92 (46/46)    | Patients treated with combination of <i>Rosa canina</i> , <i>Urtica</i> sp., <i>Harpagophytum procumbens</i> , and vitamin D (20.0 g puree and 4.0 g juice concentrate, 160 mg dry extract, 108 mg dry extract, 5 µg, respectively) or placebo for 12 weeks. WOMAC and quality of life scores significantly improved vs. placebo. | 2017 | Moré et al. [557]        |

DJD = degenerative joint diseases (osteoarthritis); MSD = musculo-skeletal disorders (low back pain); RCT = randomized controlled trial; NSAID = non-steroidal anti-inflammatory drug; WOMAC = Western Ontario and McMaster Universities.

## 12.2. Safety

A broad spectrum of claims regarding the safety of *Harpagophytum* in clinical practice can be found in the literature, ranging from unsubstantiated cautioning against its use altogether [215,558] to overly optimistic perspectives in the lay press. The truth, as it often does, lies somewhere in between.

### 12.2.1. Clinical Safety

Short- and long-term use (on average 30–60 days, in several long-term studies up to 54 weeks) have been described as safe and well-tolerated, and the most reported adverse events in clinical investigations were of mild gastrointestinal nature [559]. These may be related to its anticholinesterase effect in vitro [318,366]. A review of the safety of *Harpagophytum* preparations [560] concluded that they are likely to be safe with only few and no serious adverse events observed, however, it was also established that further, more rigorous safety investigations are required [561], especially considering that the dosage in most studies was found at the lower limit, and for the recommended long-term use.

### 12.2.2. Interaction Potential

*Harpagophytum* was found to be a weak inhibitor of CYP 1A2 and CYP 2D6, and a moderate inhibitor of CYP 2C8, CYP 2C9, CYP 2C19, and CYP 3A4 in vitro [397,399,400,562], however, clinical relevance is unlikely [402]. Increased anticoagulant effects have been reported with concurrent anticoagulant use [563–567]. While an interaction is possible, evidence is inconclusive [568] and has only been demonstrated in vitro. Herb–drug interactions and interference with anticoagulants are hypothetical and have not been conclusively demonstrated.

### 12.2.3. Adverse Event Reports

A case of hyponatremia in a patient with systemic hypertension has been associated with *Harpagophytum* (co-medications were losartan, clonidine, omeprazole, and simvastatin) [569]. Another case report suggests development of grade 2 symptomatic hypertension in a normotensive woman during self-administration of *Harpagophytum* [570]. However, available data do not suggest interaction potential with conventional antihypertensives at recommended doses (animal studies demonstrating a hypotensive effect used

much higher doses). A case-controlled surveillance study has associated *Harpagophytum* with a pancreatotoxic potential [571]. One early case report points at a potential allergic reaction after professional exposure to *Harpagophytum* [572]. Rahman and colleagues [573] included *Harpagophytum* in a review of botanicals with drug-interaction potential in the elderly with inflammatory bowel disease, however, did not present any causality that would justify concern.

#### 12.2.4. Side Effects

Considering the size of the total patient collective from all clinical investigations listed in Section 11.1. (>11,000), and the most common side effects being mild gastrointestinal complaints (nausea, abdominal pain, diarrhea), CNS disorders (dizziness, headache), and allergic skin reactions, the aforementioned case reports should be further investigated, but, until corroborated by new data, their clinical relevance can be deemed as limited.

#### 12.2.5. Pregnancy and Lactation

In Vitro data suggest spasmogenic and uterotonic effects in mammalian uterine muscles [412,413]. In the absence of adequate in vivo data [408,409], use during pregnancy and lactation should be cautioned.

### 13. Veterinary Applications

Veterinary applications of devil's claw have received increased attention and gained popularity over the last 15 years, with focus on equines and canines. Colas and colleagues [250,255,256,574] provided methods for detection and control of iridoid glucosides from *Harpagophytum* in horse urine. Torfs et al. [575] discussed the potential benefits of devil's claw products in veterinary practice and cited one study conducted by Montavon [576] in which ten horses with tarsal osteoarthritis were treated with an herbal powder mix containing *Harpagophytum* (20 g total) and smaller quantities of *Ribes nigrum*, *Equisetum arvense*, and *Salix alba* for 10 days a month over three consecutive months. The control group received 2 g of phenylbutazone daily. Locomotor scores improved significantly with the test medication vs. conventional NSAID. However, study results are of limited reliability due to size, lack of blinding, and subjective assessment. Axmann and colleagues [577,578] investigated pharmacokinetics and clinical efficacy of a *Harpagophytum* extract in horses. They provided a method with which they were able to detect harpagoside in plasma for up to 9 h after administration. Efficacy was investigated in a RCT design with 40 horses (20/20), the study medication was 10 g daily of an aqueous *Harpagophytum* extract (25.3% harpagoside) or placebo for 8 weeks, and a follow-up after 16 weeks. Locomotor abnormalities were assessed on a treadmill with an optoelectronic motion capture system, and follow-up was conducted via questionnaires. While the objective motion assessment did not yield significant differences between baseline and the end of the study, evaluation of the questionnaires reflected significant improvements and a "lingering" effect in the subjective assessment.

Moreau and colleagues [579] investigated the efficacy of *Harpagophytum* (harpagoside > 2.7%) as part of a complex mixture of ingredients for improving symptoms of canine osteoarthritis in a RCT with 32 dogs (16 per group) over 8 weeks. The primary endpoint, peak vertical force, was significantly higher in treated dogs vs. placebo after 4 and 8 weeks, and clinical signs overall improved with treatment.

Ethnoveterinary uses of devil's claw have also been recorded. Moreki [113] reports on ethnoveterinary practices in Botswana to include the use of a decoction of *Harpagophytum* in poultry.

A reliable body of clinical data confirming the efficacy of *Harpagophytum* in veterinary applications is clearly lacking but is needed to better exploit the potential benefits. In this context, it must be noted that the use of devil's claw—just like other analgesics—is highly restricted in equestrian sport. Harpagoside is included in the "Equine Prohibited Substance List" of the Federation Equestre Internationale as a "controlled medication", the

use of which is prohibited during training and competitions. Curiously, harpagoside is not included in the very same organization's "List of Detection Times", leaving horse owners in the dark as to when to discontinue use prior to a tournament. This lack of clarity may further hamper more prolific use in veterinary practice.

#### 14. Patents

As mentioned in Section 10, the majority of patents refer to processing methods, specifically extraction and dosage forms, which constitute the only legitimately patentable intellectual property for the pharmaceutical industry, except in cases where new effects or combinations, not previously described in ethnobotanical use accounts, were elucidated. It is noteworthy that most of the earlier patents listed below in Table 12 (pre-2000) have expired or been withdrawn. Pending patents have been excluded.

**Table 12.** Patents pertaining to *Harpagophytum* and its preparations.

| Title                                                                                                                                                                                                        | Date       | Number        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|---------------|
| Food supplement                                                                                                                                                                                              | 4/3/1984   | US19810287235 |
| Therapeutically active mixture                                                                                                                                                                               | 11/8/1984  | DE19833316726 |
| Homeopathic remedy for the treatment of rheumatic disorders                                                                                                                                                  | 11/19/1987 | DE19863616054 |
| Plant-based medicinal composition for internal use                                                                                                                                                           | 4/22/1988  | FR19860014608 |
| Medicinal combination based on plants and trace elements for the treatment of rheumatism and inflammatory states                                                                                             | 11/10/1988 | FR19870006450 |
| Process for the preparation, by extracting, of <i>Harpagophytum</i>                                                                                                                                          | 7/13/1992  | KR19890016112 |
| Anti-pruritic cosmetic composition containing <i>Harpagophytum</i> root extract                                                                                                                              | 1/27/1993  | EP19920402100 |
| Preparation of concentrated plant extract, particularly from <i>Harpagophytum procumbens</i>                                                                                                                 | 8/7/1997   | DE1996103788  |
| Harpagosid-angereicherter Extrakt aus <i>Harpagophytum procumbens</i> und Verfahren zu seiner Herstellung [harpagoside- enriched extract of <i>H. procumbens</i> and its manufacture]                        | 10/2/1997  | DE1996151290  |
| A purified extract from <i>Harpagophytum procumbens</i> and/or <i>Harpagophytum zeyheri</i> , a process for its preparation and its use                                                                      | 12/18/1997 | Google        |
| Skin care composition contains peroxidized fatty substance, e.g., unsaturated vegetable oils and plant extract                                                                                               | 3/20/1998  | FR19960011438 |
| Natural composition for treating bone or joint inflammation                                                                                                                                                  | 11/26/1998 | WO1998US10758 |
| Micro-nutritional compositions having a therapeutic effect containing polyunsaturated fatty acids, trace elements, and vitamins                                                                              | 7/16/1999  | FR19980000331 |
| A method of producing high anti-inflammatory activity extracts from <i>Harpagophytum procumbens</i>                                                                                                          | 10/6/1999  | GB19980006971 |
| Effervescent preparation containing a plant extract                                                                                                                                                          | 6/16/1999  | EP0922450A1   |
| Method for producing high activity extracts from <i>Harpagophytum procumbens</i>                                                                                                                             | 3/6/2001   | US19990280499 |
| Harpagoside-enriched extract from <i>Harpagophytum procumbens</i> and processes for producing the same                                                                                                       | 8/28/2001  | US19990155043 |
| Dietary supplement                                                                                                                                                                                           | 12/18/2001 | JP20000172296 |
| Pharmaceutical preparation containing <i>Cibotii rhizoma</i> and <i>Harpagophytum procumbens</i> DC extracts as main ingredients                                                                             | 6/3/2002   | KR20000071397 |
| Skin care preparation                                                                                                                                                                                        | 6/4/2002   | JP20000402968 |
| Pharmaceutical composition with anti-atherosclerotic activity                                                                                                                                                | 6/5/2002   | EP20010128629 |
| Use of harpagide-related compound as prophylactic and therapeutic agent of osteoporosis, arthritis, and disc and pharmaceutical composition containing compound as effective ingredient                      | 11/16/2002 | KR20000071497 |
| Composition useful for treating or preventing osteoarthritis, especially in horses, containing extract(s) of <i>Equisetum arvense</i> , <i>Symphytum officinale</i> , and/or <i>Harpagophytum procumbens</i> | 3/27/2003  | DE2001143146  |



Table 12. Cont.

| Title                                                                                                                                                                                                                                     | Date       | Number          |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|-----------------|
| Use of active substance mixtures containing tocopherols and <i>Harpagophytum procumbens</i> extracts for the preparation of a drug against rheumatic arthritis                                                                            | 12/17/2003 | EP20020012765   |
| Chewing gum composition with vegetal additives                                                                                                                                                                                            | 7/29/2004  | WO2003EP14600   |
| Pain-relieving agent containing extract of <i>Harpagophytum procumbens</i> , <i>Corydalis turtschanovii</i> , and <i>Atractylodes japonica</i>                                                                                            | 2/5/2005   | KR20030052489   |
| Treating or preventing renal diseases, dysfunction, and/or damage, e.g., degenerative and/or inflammatory renal disease, using <i>Harpagophytum</i> extract or harpagoside                                                                | 3/10/2005  | DE2003126556    |
| Phyto-composition for the treatment of articular diseases                                                                                                                                                                                 |            | WO2005092355    |
| Use of devil's claw ( <i>Harpagophytum procumbens</i> ) root extracts for endometriosis treatment                                                                                                                                         | 11/2/2006  | WO2006EP61831   |
| A method for separating harpagide from <i>Harpagophytum procumbens</i>                                                                                                                                                                    | 2/5/2007   | KR20050102609   |
| Activator of peroxisome proliferator-activated receptor (PPAR)                                                                                                                                                                            | 5/17/2007  | JP20050317156   |
| Adjuvant composition for physiotherapy                                                                                                                                                                                                    | 7/24/2007  | KR20060005183   |
| Maillard reaction inhibitor, skin care preparation containing the same, and food and beverage                                                                                                                                             | 10/4/2007  | JP20060080104   |
| Phyto-composition for the treatment of joint diseases                                                                                                                                                                                     | 12/13/2007 | US20050594439   |
| Natural remedy—dietary supplement combination product                                                                                                                                                                                     | 9/4/2008   | US20060815432   |
| Root extract of <i>Harpagophytum</i> for stimulating hair growth                                                                                                                                                                          | 5/27/2009  | EP20070802633   |
| Skin care preparation, oral composition, and food and drink                                                                                                                                                                               | 10/22/2009 | JP20080091677   |
| Novel method for preparing purified extracts of <i>Harpagophytum procumbens</i>                                                                                                                                                           | 12/9/2010  | US20080599146   |
| Animal food compositions                                                                                                                                                                                                                  | 7/21/2011  | WO2010US60804   |
| Compositions comprising plant extracts and use thereof for treating inflammation                                                                                                                                                          | 10/27/2011 | US200913120739  |
| Anti-inflammatory composition                                                                                                                                                                                                             | 12/21/2011 | EP20110170436   |
| Antirheumatic body cream composition                                                                                                                                                                                                      | 12/30/2011 | RO20110000644   |
| Pharmaceutical composition for preventing and treating metabolic bone disease comprising of <i>Harpagophytum</i>                                                                                                                          | 6/18/2012  | KR20110147135   |
| Phyto-concentrated composition, useful as antispasmodic relaxant, and muscular comfort to, e.g., enhance relaxation of painfully contracted muscle tissue, comprises, e.g., cannabis sativa and an excipient comprising, e.g., castor oil | 10/12/2012 | FR20110001030   |
| Nonabrasive toothpaste containing enzyme papain, <i>Harpagophytum</i> extract d,l-pyrrolidone carboxylate n-cocoyl ethyl arginate, and sodium fluoride                                                                                    | 7/20/2013  | RU20120101119   |
| Cosmetic composition for calming and applying an electric current of skins and manufacturing the same                                                                                                                                     | 12/27/2013 | KR20120065152   |
| Anti-rheumatism medicinal liquor and preparation method thereof                                                                                                                                                                           | 3/19/2014  | CN20131645408   |
| Composition containing chondroitin sulfate and hyaluronidase                                                                                                                                                                              | 12/10/2014 | RU20130123301   |
| Mucoadhesive devil's claw extracts ( <i>Harpagophytum procumbens</i> ) and uses thereof                                                                                                                                                   | 3/11/2015  | EP20140184267   |
| Compositions for alleviating, preventing, or treating pain comprising <i>Harpagophytum procumbens</i> and <i>Acanthopanax senticosus</i> extracts as active ingredients                                                                   | 6/8/2015   | KR20130146128   |
| Traditional Chinese medicine composite for treating gout                                                                                                                                                                                  | 7/8/2015   | CN20151209743   |
| Cell line cultures from plants belonging to the <i>Harpagophytum</i> genus                                                                                                                                                                | 1/4/2018   | WO2017EP65814   |
| Method for preparing purified extracts of <i>Harpagophytum procumbens</i>                                                                                                                                                                 | 30/10/2018 | US20100311675A1 |
| Oral herbal pain killer formulations                                                                                                                                                                                                      | 15/10/2020 | WO2020208395A1  |
| Polyherbal transdermal patch for pain management and its process of preparation                                                                                                                                                           | 22/10/2020 | WO2020212820A2  |
| External medicine for inhibiting postoperative venous thrombosis and application thereof                                                                                                                                                  | 19/2/2021  | CN109589331B    |
| Freedom (nutritional supplement)                                                                                                                                                                                                          | 9/2/2021   | US20200060320A1 |

## 15. Discussion and Conclusions

Devil's claw is a well-established phytopharmaceutical. A large body of data exists in which composition, pharmacological activities, and clinical effects are elucidated, and in turn support and affirm traditional use applications. Nonetheless, several aspects requiring further investigation were highlighted by this review.

Revision of the genus to account for introgression, geographical, and biochemical variation, and geo-authenticity is needed.

In view of the interchangeable use of both *Harpagophytum* species and mixtures thereof in clinical practice, further comparative examination of the composition of both species is needed. Verbascoside as an anti-inflammatory compound present in *Harpagophytum* could be an interesting target of future research.

Despite some inconsistent outcomes and contradictory results, pharmacological evidence appears to be overall sufficient to support clinical use. Sufficient pharmacological differentiation between *Harpagophytum* species, however, is lacking.

Toxicological evaluations of *Harpagophytum* indicate a low toxicity in animal models. While genotoxicity testing is part of the regulatory requirements for the market authorization of herbal medicinal products in Europe, results are proprietary (product-related) and have not been published. Adequate tests on reproductive toxicity, genotoxicity, and carcinogenicity, performed according to currently valid OECD guidelines, need to be made publicly available.

While there may be strong clinical evidence that devil's claw preparations are effective in the treatment of degenerative joint diseases and musculoskeletal disorders in principle, this conclusion cannot be extended to specific preparations, because of the varying pharmaceutical quality of individual preparations.

Further investigations are required (a) to identify the therapeutically active substances or fractions and thus enable tests which (b) use accordingly standardized and sufficiently dosed preparations with a carefully designed setup and methodology in order to obtain quantifiable results for the efficacy of devil's claw preparations. These need to be conducted with both *Harpagophytum* spp. individually but prepared identically. Trial designs should be guided by the recommendations of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). Specifically, both species could be compared in a two-arm cross-over design. Conventional medication could be added as a third arm to assess comparative efficacy. Studies should be of adequate power, randomized, placebo-controlled, and double-blinded. Problematic in an ethical sense is the denial of "first aid" medication in placebo-controlled studies, permission of which would confound outcomes. Outcomes should be objective or at least a combination of objective and subjective measures.

Further research is also warranted in the area of clinical safety, specifically with regard to the drug interaction potential of devil's claw preparations. Until then, safety considerations as expressed in current compendia, e.g., [15], should be considered appropriate.

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